FORM PTO-1390 (Modified) (REV 11-2000) U.S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U S APPLICATION NO (IF KNOWN, SEE 37 CFR
217925US0XPCT	10/030269

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/04515	6 July 2000	8 July 1999 (earliest)

TITLE OF INVENTION
AMYLOID-BETA PROTEIN AGGREGATION- REGULATING FACTORS

APPLICANT(S) FOR DO/EO/US
OTA Toshio et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1 97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Request for Priority Under 35 U.S.C 119
Request for Priority Under 35 U.S.C 119(e)
Sequence Listing (34 pages)
Form PTO-1449

U.S. APPLICATION NO (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/030269	PCT/JP00/04515	217925US0XPCT

24. The following fees are submitted..		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1 445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1040.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$890.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$740.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (c)).		**$130.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	- 20 =	0	x	$18.00	**$0.00**
Independent claims	- 3 =	0	x	$84.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.				☐	**$0.00**

TOTAL OF ABOVE CALCULATIONS =		**$1,020.00**
☐ Applicant claims small entity status. See 37 CFR 1.27) The fees indicated above are reduced by 1/2.		**$0.00**
SUBTOTAL =		**$1,020.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +		**$0.00**
TOTAL NATIONAL FEE =		**$1,020.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐		**$0.00**
TOTAL FEES ENCLOSED =		**$1,020.00**
	Amount to be: refunded	$
	charged	$

a. ☒ A check in the amount of **$1,020.00** to cover the above fees is enclosed.

b ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

22850

SIGNATURE

Norman F. Oblon

NAME

24,618

REGISTRATION NUMBER ~~James D. Hamilton~~ Registration No. 28,421

1/8/02

DATE

PCT

Docket No. 217925US0XPCT

IN RE APPLICATION OF: Toshio OTA et al

SERIAL NO: 10/030,269

FILED: January 8, 2002

FOR: AMYLOID-BETA PROTEIN AGGREGATION-REGULATING FACTORS

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Transmitted herewith is an amendment in the above-identified application.

- ☐ No additional fee is required
- ☐ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 is claimed.
- ■ Additional documents filed herewith: Notice to File Missing Parts - Return Copy; Request for Extension of Time (One-Month); Filing of Declaration under 37 CFR 1.53(f); Declaration and Power of Attorney, 20 pages (Executed); Declaration of Yuri HIO, 1 page (Executed); Sequence Listing (Paper); Computer-Readable Sequence Listing (Diskette); Preliminary Amendment and Statement w/Marked-up copy

The Fee has been calculated as shown below:

CLAIMS	CLAIMS REMAINING		HIGHEST NUMBER PREVIOUSLY PAID	NO. EXTRA CLAIMS	RATE	CALCULATIONS
TOTAL	51	MINUS	20	31	× $18 =	$558.00
INDEPENDENT	2	MINUS	3	0	× $84 =	$0.00
		■ MULTIPLE DEPENDENT CLAIMS			+ $280 =	$280.00
		TOTAL OF ABOVE CALCULATIONS				$838.00
		☐ Reduction by 50% for filing by Small Entity				$0.00
		☐ Recordation of Assignment			+ $40 =	$0.00
					TOTAL	$838.00

- ■ A check in the amount of **$948.00** is attached.
- ■ Please charge any additional Fees for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.
- ■ If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. §1.136, and any additional fees required under 37 C.F.R. §1.136 for any necessary extension of time may be charged to Deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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07/03/2002 HKAYPAGH 00000073 10030269

01 FC:965 558.00 OP
02 FC:966 280.00 OP

Adjustment date: 07/18/2002 RWHITE1
07703/2002 HKAYPAGH 00000073 10030269
02 FC:968 -280.00 OP

Repln. Ref: 07/18/2002 RWHITE1 0017375100
DA#:150030 Name/Number:10030269
FC: 704 $280.00 CR

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Docket No.: 217925US0XPCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

Toshio OTA, et al. : ATTN: BOX SEQUENCE

SERIAL NO: 10/030,269 :

FILED: JANUARY 8, 2002 :

FOR: AMYLOID-BETA PROTEIN AGGREGATION-REGULATING FACTORS

PRELIMINARY AMENDMENT AND STATEMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

In response to the Office Correspondence mailed August 8, 2002, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown in the marked-up copy to read as follows:

--18. (Amended) An isolated polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.--

--24. (Amended) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and

recovering the expression product.

25. (Amended) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and

recovering the expression product.--

--27. (Amended) An immunological assay comprising the step of monitoring an immunological reaction between the protein according to claim 19 and the antibody against the protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.

28. (Amended) A method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to claim 18, wherein said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid-β protein, and,

(b) selecting the candidate compound that regulates the aggregation or deposition of amyloid-β protein.--

--37. (Amended) An isolated polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.--

--42. (Amended) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.

43. (Amended) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.--

--45. (Amended) An immunological assay comprising the step of: monitoring an immunological reaction between the peptide according to claim 38 and the antibody against the peptide encoded by the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

46. (Amended) A method of screening for a compound that regulates the activity of a peptide encoded by the polynucleotide according to claim 37, wherein, said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid-β protein, and,

(b) selecting the candidate compound that regulates the aggregation or deposition of amyloid-β protein.--

REMARKS

Claims 18-68 are active in the present application. The amendments contained herein serve only to correct minor typographical errors. No new matter is believed to have been added by this amendment.

Applicants have now submitted a substitute computer-readable Sequence Listing. The sequence information recorded in the substitute computer-readable Sequence Listing is identical to the paper copy of the substitute Sequence Listing filed on June 27, 2002, a copy of which is enclosed herewith for the Office's convenience, along with the date-stamped filing receipt evidencing timely filing thereof. No new matter is believed to have been introduced by the submission of the substitute Sequence Listing and the corresponding computer-readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits.

Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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Docket No.: 217925US-0XPCT
Serial No.: 10/030,269

MARKED-UP COPY

IN THE CLAIMS

Please amend the claims as follows:

--18. (Amended) An isolated polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.--

--24. (Amended) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring a polynucleotide

encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and

recovering the expression product.

25. (Amended) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and

recovering the expression product.--

--27. (Amended) An immunological assay comprising the step of monitoring an immunological reaction between the protein according to claim 19 and the antibody against the protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.

28. (Amended) A method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to claim 18, wherein said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid-β protein, and,

(b) selecting [a] the candidate compound that regulates the aggregation or deposition of amyloid-β protein.--

--37. (Amended) An isolated polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.--

--42. (Amended) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.

43. (Amended) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.--

--45. (Amended) An immunological assay comprising the step of: monitoring an immunological reaction between the peptide according to claim 38 and the antibody against the peptide encoded by the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or

deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

46. (Amended) A method of screening for a compound that regulates the activity of a peptide encoded by the polynucleotide according to claim 37, wherein, said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid-β protein, and,

(b) selecting [a] the candidate compound that regulates the aggregation or deposition of amyloid-β protein.--

Docket No.: 217925US0XPCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

Toshio OTA, et al. : ATTN: BOX SEQUENCE

SERIAL NO: 10/030,269 :

FILED: JANUARY 8, 2002 :

FOR: AMYLOID-BETA PROTEIN AGGREGATION-REGULATING FACTORS

PRELIMINARY AMENDMENT AND STATEMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

In response to the Office Correspondence mailed March 27, 2002, please amend the above-identified application as follows.

IN THE TITLE

Please delete the title on page 1, line 3 and replace with the following title.

AMYLOID-β PROTEIN AGGLUTINATION-CONTROLLING FACTOR

IN THE SPECIFICATION

Please replace the paragraph on page 25, lines 27-33 with the following paragraph.

NT-2 neuron progenitor cells (Stratagene) a teratocarcinoma cell line from human embryo testis, which can differentiate into neurons when treated with retinoic acid, were used. The NT-2 cells were cultured according to the manufacturer's instructions,

(1) without retinoic acid treatment (NT2RM1),

(2) 2 weeks after retinoic acid was added to cultured NT-2 cells (NT2RP3)

Please replace the paragraph on page 29, lines 27-28 with the following paragraph.

Example 2: Expression of the proteins promoting or preventing amyloid β protein aggregation

Please replace line 1 on page 30 with the following line.

Example 3: Amyloid β aggregation reaction

Please replace the paragraph on page 30, lines 2-12 with the following paragraph.

The supernatants obtained in Example 2 were used to screen for proteins that promote or suppress amyloid β protein aggregation. In principle, the experiments were conducted according to Methods in Enzymology Volume 309 (1999) p 274-284. Instead of Aβ40 and Aβ42, which are commonly found in vivo, Aβ1-28 consisting of 28 amino acid residues from the N-terminus of Aβ, which is considered to aggregate to a similar extent as Aβ40 and Aβ42, was used in the experiments. Experiments as shown below were conducted, and as a result, five clones showing augmented promotion or suppression of aggregation were selected from 108 clones. Experiment method and the activities of the five selected clones are shown below.

Please replace the paragraph on page 31, lines 10-11 with the following paragraph.

Example 4: Gene Expression analysis in patients with Alzheimer's disease

Please delete the original Sequence Listing.

Page 37 (Abstract), after the last line, beginning on a new page, please insert the attached Sequence Listing.

IN THE CLAIMS

Please cancel Claims 1-17.

Please add the following new claims.

18. (New) An isolated polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.

19. (New) A protein encoded by a polynucleotide according to claim 18.

20. (New) A protein that suppresses or promotes the aggregation of amyloid-β protein, wherein said protein is encoded by a polynucleotide that, from a molecular

evolutionary aspect, originated from the same gene from which a polynucleotide according to claim 1 originated from.

21. (New) A vector comprising a polynucleotide according to claim 18.

22. (New) A transfectant harboring a polynucleotide according to claim 18.

23. (New) A transfectant harboring the vector according to claim 21.

24. (New) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and

recovering the expression product.

25. (New) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising a

polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and

recovering the expression product.

26. (New) An antibody against the protein according to claim 19.

27. (New) An immunological assay comprising the step of monitoring an immunological reaction between the protein according to claim 19 and the antibody against the protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.

28. (New) A method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to claim 18, wherein said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid-β protein, and,

(b) selecting a the candidate compound that regulates the aggregation or deposition of amyloid-β protein.

29. (New) A method of screening for a compound that regulates expression of a protein encoded by a polynucleotide according to claim 18, wherein said method comprises the following steps of:

(a) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:

(i) an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and,

(ii) a reporter gene operably linked downstream of the expression regulatory region,

(b) measuring the presence of the reporter gene, and,

(c) selecting the candidate compound that increases or decreases the reporter activity measured in step (b) when compared to the control.

30. (New) A pharmaceutical agent comprising a compound obtained by the method according to claim 28.

31. (New) A pharmaceutical agent comprising the protein according to claim 19.

32. (New) A pharmaceutical agent comprising the protein according to claim 20.

33. (New) A pharmaceutical agent comprising an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to claim 18.

34. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 28.

35. (New) A method for detecting Alzheimer's disease, comprising the following steps of:

(a) measuring the expression of a polynucleotide according to claim 18,

(b) comparing the measurement obtained in (a) with that obtained when the polynucleotide is expressed in healthy subjects and detecting a change in expression,

(c) linking Alzheimer's disease with said change in expression of the polynucleotide.

36. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient a compound obtained by the method according to claim 28.

37. (New) An isolated polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

38. (New) A peptide encoded by the polynucleotide according to claim 37.

39. (New) A vector comprising the polynucleotide according to claim 37.

40. (New) A transfectant harboring the polynucleotide according to claim 37.

41. (New) A transfectant harboring the vector according to claim 39.

42. (New) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.

43. (New) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding

a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.

44. (New) An antibody against the peptide according to claim 38.

45. (New) An immunological assay comprising the step of: monitoring an immunological reaction between the peptide according to claim 38 and the antibody against the peptide encoded by the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid-β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

46. (New) A method of screening for a compound that regulates the activity of a peptide encoded by the polynucleotide according to claim 37, wherein, said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid-β protein, and,

(b) selecting a the candidate compound that regulates the aggregation or deposition of amyloid-β protein.

47. (New) A method of screening for a compound that regulates expression of a peptide encoded by a polynucleotide according to claim 37, wherein said method comprises the following steps of:

(a) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:

(i) an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and,

(ii) a reporter gene operably linked downstream of the expression regulatory region,

(b) measuring the presence of the reporter gene, and,

(c) selecting the candidate compound that increases or decreases the reporter activity measured in step (b) when compared to the control.

48. (New) A pharmaceutical agent comprising a compound obtained by the method according to claim 46.

49. (New) A pharmaceutical agent comprising the peptide according to claim 38.

50. (New) A pharmaceutical agent comprising an antisense polynucleotide complementary to the protein-coding sequence of the polynucleotide according to claim 37.

51. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 46.

52. (New) A method for detecting Alzheimer's disease, comprising the following steps of:

(a) measuring the expression of a polynucleotide according to claim 37,

(b) comparing the measurement obtained in (a) with that obtained when the polynucleotide is expressed in healthy subjects and detecting a change in expression,

(c) linking Alzheimer's disease with said change in expression of the polynucleotide.

53. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient a compound obtained by the method according to claim 46.

54. (New) A polynucleotide comprising a polynucleotide according, or a nucleotide sequence complementary to the complementary strand of the polynucleotide, according to claim 18, wherein said polynucleotide comprises at least 15 nucleotides.

55. (New) A pharmaceutical agent comprising a compound obtained by the method according to claim 29.

56. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 29.

57. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a protein according to claim 19.

58. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a protein according to claim 20.

59. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient a compound obtained by the method according to claim 29.

60. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient the protein according to claim 19.

61. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient the protein according to claim 20.

62. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to claim 18.

63. (New) A pharmaceutical agent comprising a compound obtained by the method according to claim 47.

64. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 47.

65. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a peptide according to claim 38.

66. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient a compound obtained by the method according to claim 47.

67. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient the peptide according to claim 38.

68. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to claim 37.

REMARKS

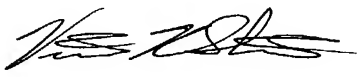
Claims 18-68 are active in the present application. Claims 1-17 have been cancelled. Claims 18-68 are new claims. Support for the new claims is found in the original claims and throughout the specification. New Claims 37-54 are drawn to a partial peptide. Support for claims to a partial peptide can be found in the specification on page 8, lines 21-23. No new matter is believed to have been added by this amendment.

Applicants have now submitted a substitute Sequence Listing and a corresponding computer-readable Sequence Listing. The sequence information recorded in the corresponding computer-readable Sequence Listing is identical to the paper copy of the substitute Sequence Listing. Support for all of the sequences listed in the substitute Sequence Listing is found in the present application as originally filed. No new matter is believed to have been introduced by the submission of the substitute Sequence Listing and the corresponding computer-readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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22850

Docket No.: 217925US-0XPCT
Serial No.: 10/030,269

MARKED-UP COPY

IN THE TITLE

Please delete the title on page 1, line 3 and replace with the following title.

[AMYLOID-β PROTEIN AGGREGATION-REGULATING FACTORS]

--AMYLOID-β PROTEIN AGGLUTINATION-CONTROLLING FACTOR--

IN THE SPECIFICATION

Please replace the paragraph on page 25, lines 27-33 with the following paragraph.

--NT-2 neuron progenitor cells (Stratagene) a teratocarcinoma cell line from human embryo testis, which can differentiate into neurons when treated with retinoic acid, were used. The NT-2 cells were cultured according to the manufacturer's instructions,

(1) without retinoic acid treatment (NT2RM1),

[(3)] (2) 2 weeks after retinoic acid was added to cultured NT-2 cells (NT2RP3)--

Please replace the paragraph on page 29, lines 27-28 with the following paragraph.

--Example [5] 2: Expression of the proteins promoting or preventing amyloid β protein aggregation--

Please replace line 1 on page 30 with the following line.

--Example [6] 3: Amyloid β aggregation reaction--

Please replace the paragraph on page 30, lines 2-12 with the following paragraph.

--The supernatants obtained in Example [5] 2 were used to screen for proteins that promote or suppress amyloid β protein aggregation. In principle, the experiments were

conducted according to Methods in Enzymology Volume 309 (1999) p 274-284. Instead of Aβ40 and Aβ42, which are commonly found in vivo, Aβ1-28 consisting of 28 amino acid residues from the N-terminus of Aβ, which is considered to aggregate to a similar extent as Aβ40 and Aβ42, was used in the experiments. Experiments as shown below were conducted, and as a result, five clones showing augmented promotion or suppression of aggregation were selected from 108 clones. Experiment method and the activities of the five selected clones are shown below.--

Please replace the paragraph on page 31, lines 10-11 with the following paragraph.

--Example [6] 4: Gene Expression analysis in patients with Alzheimer's disease--

Please delete the original Sequence Listing.

Page 37 (Abstract), after the last line, beginning on a new page, please insert the attached Sequence Listing.

IN THE CLAIMS

Claims 1-17 (Cancelled).

Claims 18-68 (New).

22850

DESCRIPTION

AMYLOID-β PROTEIN AGGREGATION-REGULATING FACTORS

Technical Field

The present invention relates to proteins that suppress or promote the aggregation or deposition of amyloid-β protein (also referred to as "Aβ" hereinafter), polynucleotides encoding the proteins, a method for preparing the proteins using the polynucleotides, an expression system for producing the proteins, and a method of screening for a compound that suppresses or promotes the aggregation of amyloid-β protein using the expression system. The present invention also relates to a method for preventing and treating Alzheimer's disease using proteins obtained by the method above, or a compound obtained by the screening method.

Background Art

Alzheimer's disease is a disorder associated with cognitive dysfunctions, and is characterized by a loss of nerve cells and emergence of a large number of senile plaques and neurofibrillary tangles. Senile plaques are detected at the earliest stage of development of this disease. These plaques are highly specific to this disease since they are not found in other neurodegenerative disorders. Amyloid-β protein (Aβ) is the major constituent of senile plaques and forms amyloid fibrils having a β-sheet structure. Aβ is a polypeptide comprising approximately 40 amino acid residues and has a molecular weight of 4,000 Da. It easily aggregates to form fibrils and becomes insoluble. The major molecular species of this protein are Aβ40, which ends with valine at amino acid residue 40, and Aβ42, the longer form of Aβ having two additional residues. Although Aβ is usually degraded and never accumulates in the brain, the degrading capacity decreases with aging, causing an accumulation of Aβ. This triggers neuronal dysfunction and cell death, ultimately resulting in dementia and Alzheimer's disease. Through various genetic analyses and molecular biological and neuropharmacological studies, "amyloid hypothesis" has been proposed as a cause of the pathogenesis of Alzheimer's disease.

Disclosure of the Invention

An objective of the present invention is to provide proteins that suppress or promote aggregation or deposition of amyloid-β protein, and polynucleotides encoding these proteins. A further objective of the present invention is to provide a method for treating Alzheimer's disease by discovering a method or substance that suppresses or promotes aggregation or deposition of amyloid-β protein.

To achieve the above objectives, the present inventors conducted extensive studies and finally discovered polynucleotides encoding secretory or membrane-bound forms of proteins that suppress or promote the aggregation or deposition of amyloid-β protein, and hence completed the present invention.

Thus, the present invention relates to:

[1] a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:,

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9;

[2] a polynucleotide encoding a partial peptide of the protein encoded by a polynucleotide according to [1];

[3] a peptide or protein encoded by a polynucleotide according to [1] or [2];

[4] a protein that suppresses or promotes the aggregation of amyloid-β

protein, wherein said protein is encoded by a polynucleotide that, from a molecular evolutionary aspect, originated from the same gene from which a polynucleotide according to [1] originated from;

[5] a vector comprising a polynucleotide according to [1] or [2];

[6] a transfectant harboring a polynucleotide according to [1] or [2] or the vector according to [5];

[7] a method for producing the peptide or protein according to [3], wherein said method comprises the steps of: culturing the transfectant according to [6], and recovering the expression product;

[8] a polynucleotide comprising a polynucleotide according to [1] or [2] or a nucleotide sequence complementary to the complementary strand of the polynucleotide according to [1] or [2], wherein said polynucleotide comprises at least 15 nucleotides;

[9] an antibody against the peptide or protein according to [3];

[10] an immunological assay comprising the step of: monitoring an immunological reaction between the peptide or protein according to [3] and the antibody according to [9];

[11] a method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to [1], wherein said method comprises the following steps of:

contacting a candidate compound with a protein encoded by a polynucleotide according to [1], or with a cell expressing said protein, in the presence of amyloid-β protein, and,

selecting a the candidate compound that regulates the aggregation or deposition of amyloid-β protein;

[12] a method of screening for a compound that regulates expression of a protein encoded by a polynucleotide according to [1], wherein said method comprises the following steps of:

(1) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:

an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and,

a reporter gene operably linked downstream of the expression regulatory region,

(2) measuring the activity of the reporter gene, and,

(3) selecting the candidate compound that increases or decreases the reporter activity measured in step (b) when compared to the control;

[13] a pharmaceutical agent comprising a compound obtained by the method according to [11] or [12];

[14] a pharmaceutical agent comprising the peptide or protein according to [3] or [4];

[15] a pharmaceutical agent comprising an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to [1];

[16] the pharmaceutical agent according to [13] or [14], wherein said pharmaceutical agent is a preventive or therapeutic agent for Alzheimer's disease; and,

[17] a method for detecting Alzheimer's disease, comprising the following steps of:

(1) measuring the expression of a polynucleotide according to [1];

(2) comparing the measurement obtained by (1) with that obtained when the polynucleotide is expressed in healthy subjects; and,

(3) linking Alzheimer's disease with said change in expression of the polynucleotide.

The proteins of the present invention that suppress or promote the aggregation of amyloid-β protein, and the polynucleotides encoding the proteins comprise the whole or part of the sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9.

The polynucleotides of the present invention may include any nucleotide that can encode the proteins of the present invention, such as genomic DNA and chemically-synthesized DNA as well as cDNA, but are not limited thereto. The polynucleotides of the present invention may also include polynucleotides having any nucleotide sequence that is based on the degeneracy of the genetic code, as long as the polynucleotides encode the proteins of the present invention. The polynucleotides encoding the proteins of the present invention may be isolated by conventional methods, such as hybridization using as a probe a polynucleotide sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9, or a partial sequence thereof, or PCR using primers designed

based on the information of these sequences.

A protein of the present invention that suppresses or promotes amyloid-β protein aggregation, can be obtained by expressing the protein in a transformant using an expression vector comprising the open reading frame within the sequence shown in, for example, SEQ ID NO. 1, 3, 5, 7 or 9. These expressed proteins may be purified and isolated, using conventional methods, from the culture or cell fraction. Specifically, methods for purification and isolation are, for example, as follows: first, the cells or supernatant is collected using conventional methods, such as filtration and centrifugation, and the cell membranes and/or the cell walls are then treated by sonication and/or with lysozyme to obtain a cell membrane fraction. Subsequently, the cell membrane fraction thus obtained is dissolved in a suitable solution. From the supernatant or the cell membrane fraction, the protein of the invention is isolated and purified according to conventional methods generally used for purification and isolation of a natural or synthetic protein. Examples of methods for isolation or purification include dialysis, gel filtration, affinity chromatography using a monoclonal antibody against the proteins of the present invention or a partial peptide thereof, column chromatography using an appropriate absorbent, high performance liquid chromatography, etc.

Furthermore, the present invention includes polynucleotides encoding proteins functionally equivalent to the proteins described above. As used herein, the term "functionally equivalent" means that the protein of interest has an activity that suppresses or promotes amyloid-β protein aggregation. The activity that suppresses or promotes amyloid-β protein aggregation can be confirmed by using, for example, the methods described in the working examples. Aβ and its fragments are prone to aggregate under particular conditions. Addition of a test compound under such conditions would give rise to Aβ aggregates, if the test compound had a property that promotes aggregation. A fragment comprising the N-terminal amino acid sequence (residues 1-28) of Aβ has been used in experiments of this sort as a partial peptide having Aβ-aggregating activity (Methods in Enzymology Vol. 309, 274-284, 1999). Aβ aggregation can be detected optically,

or can be confirmed microscopically after staining with Congo red and such.

One skilled in the art would be able to prepare proteins functionally equivalent to the proteins used in the β-amyloid aggregation tests described in the working examples below, for example, by using a method for introducing mutations into the amino acid sequences of proteins (e.g. site-directed mutagenesis, Current Protocols in Molecular Biology edit. Ausubel et al. (1987) Publish. John Wily & Sons Section 8.1-8.5). Such proteins might occur due to spontaneous mutation of amino acids in nature. The present invention also includes a protein having an amino acid sequence in which one or several amino acid residues are different from those found in a sequence of any one of the proteins identified in the working examples below (SEQ ID NO. 2, 4, 6, 8 or 10, or the amino acid sequence encoded by SEQ ID NO. 1, 3, 5, 7 or 9) due to a substitution, deletion, insertion and/or addition, as long as the protein retains a function equivalent to the proteins identified in the working examples below.

Number or sites of amino acid mutations in the protein are not limited, as long as the protein function is retained. The number (percentage) of mutations is typically 10% or less, preferably 5% or less, and more preferably 1% or less of the total amino acids. Alternatively, the mutation of "several" amino acids as used in the present invention includes the mutation of a "few" amino acids as well. "Few" refers to, for example, five, four, three, two, or one amino acid. Preferably, in view of maintaining protein function, substituting amino acids may have properties similar to the amino acids to be substituted. For example, Ala, Val, Leu, Ile, Pro, Met, Phe, and Trp are all classified into nonpolar amino acids, and they are thought to share common properties. Uncharged amino acids include Gly, Ser, Thr, Cys, Tyr, Asn, and Gln. Acidic amino acids include Asp and Glu, and basic amino acids include Lys, Arg, and His.

Alternatively, a protein functionally equivalent to the protein identified in the working examples below can be isolated using a hybridization or gene amplification technique well known to one skilled in the art. More specifically, using the hybridization technique (Current Protocols in Molecular Biology edit. Ausubel et al. (1987)

Publish. John Wily & Sons Section 6.3-6.4), one skilled in the art would routinely be able to isolate a polynucleotide showing a significant homology to any one of the polynucleotide sequences encoding the proteins identified in the working examples below (SEQ ID NO. 1, 3, 5, 7 or 9) by using a polynucleotide sequences, or a portion thereof, and obtain a functionally equivalent protein from the polynucleotide isolated. The present invention includes a protein encoded by a polynucleotide hybridizing to a polynucleotide encoding a protein identified in the working examples below, as long as the proteins are functionally equivalent . A functionally equivalent protein can be isolated from animals including, but not limited to, vertebrates such as humans, mice, rats, rabbits, pigs, and cattle. From these animals, one can isolate genes that originated from molecular-evolutionarily the same gene that encodes a protein of the present invention that suppresses or promotes amyloid β protein aggregation. As used herein, the term "genes that originated from molecular-evolutionarily the same gene" refers to genes that are rationally judged to have evolved from one ancestor gene from which the human gene of the present invention evolved in the course of molecular-evolution. This judgment is based on polynucleotide sequence analysis of the genes or analysis of their physiological roles and such. Such genes maintain a significant nucleotide sequence homology among them.

Stringent hybridization conditions for isolating a polynucleotide encoding a functionally equivalent protein are, typical washing conditions such as "1× SSC, 0.1% SDS, 37℃". More stringent conditions are, for example, "0.5× SSC, 0.1% SDS, 42℃", and even more stringent conditions are, for example, "0.1× SSC, 0.1% SDS, 65℃". The more stringent the hybridization conditions become, the more homologous to the probe sequence the polynucleotide is expected to be. Note that the above combinations of SSC, SDS, and temperature are given only for illustration, and one skilled in the art can achieve the same level of stringency by combining these factors appropriately to determine the hybridization conditions. The factors include those described above, or other factors (e.g. probe concentrations, length of probes, reaction time, etc.).

In general, a protein isolated using such hybridization techniques shows a significant homology in the nucleotide sequence encoding the protein, or in its amino acid sequence, compared to the sequence of a protein of the present invention, shown in SEQ ID NO. 2, 4, 6, 8 or 10, or a protein encoded by the a sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9. "Significant homology" refers to a sequence identity of at least 60% or more, preferably 70% or more, more preferably 80% or more, even more preferably 90% or more, and most preferably 95% or more. Sequence homology can be determined using the BLAST 2 search algorithm (Altschul, S.F. et al, 1997, Gapped BLAST and PSI-BLAST: a new generation of protein database search programs, Nucleic Acids Res. 25: 3389-3402).

A gene-amplification technique (PCR) (Current protocols in Molecular Biology edit. Ausubel et al. (1987) Publish. John Wiley & Sons Section 6.1-6.4) can be used to design primers based on a part of any of the polynucleotide sequences identified in the working examples below (SEQ ID NO. 1, 3, 5, 7 or 9), and to isolate a polynucleotide fragment that shows a significant homology to the above polynucleotide sequence or a portion thereof, to obtain a protein functionally equivalent to the protein identified in the working examples.

The present invention also relates to a partial peptide of the proteins of the present invention and to a polynucleotide encoding the partial peptide. A partial peptide of the present invention comprises at least 7 amino acid residues, preferably 9 or more amino acid residues, more preferably 12 or more amino acid residues, even more preferably 15 or more amino acid residues. The partial peptide of the present invention may be produced by, for example, genetic engineering, a well-known technique for peptide synthesis, or cleavage of the proteins of the present invention with an appropriate peptidase.

The present invention also provides expression vectors comprising any one of the polynucleotides mentioned above. Furthermore, the present invention relates to transfectants harboring any of the expression vectors or polypeptides mentioned above, and a method for producing proteins or partial peptides thereof that suppress or promote amyloid-β protein aggregation. Such a method comprises culturing the transfectant and isolating a protein of the

present invention from the culture. Moreover, the present invention provides the protein or partial peptide produced by the above method.

When producing polypeptides by means of genetic recombination, the type and extent of glycosylation of a polypeptide of interest would differ depending on the type of host cell. Furthermore, in the method of so-called "secretory production" of polypeptides, it is well known to one skilled in the art that (N- and/or C-) terminal amino acid sequences of precursor peptides expressed in host cells would undergo processing by signal peptidases and such to produce polypeptides having various terminal sequences. Therefore, one skilled in the art would easily understand that such polypeptides are also included in the proteins of the present invention.

The working examples described below illustrates only an example of constructing a vector that functions in mammalian cells as an expression vector. However, since the polynucleotide sequences encoding the proteins of the present invention are disclosed herein, it would be easy for one skilled in the art to construct an expression vector that can express and produce a protein of the present invention when such a vector is introduced into a fungal host cell, such as a yeast, or a prokaryotic host cell. Therefore, the present invention includes expression vectors constructed using any methods known in the art based on the polynucleotide sequences of the present invention.

Microbial cells that can be used for the expression of the polynucleotides encoding the proteins of the present inventions include, for example, prokaryotic bacteria (e.g. Escherichia coli and Bacillus subtilis) and eukaryotic yeasts (e.g. Saccharomyces cerevisiae). Mammalian cells include cultured human cells and cultured animal cells. Moreover, cultured plant cells can be used.

Examples of microorganisms include bacteria of the genus Escherichia (e.g. E. coli HB101 ATCC 33694, E. coli HB101-16 FERM BP-1872, E. coli MM294 ATCC 31446, E. coli DH1 ATCC 33849, etc.) and baker's yeast (e.g. S. cerevisiae AH22 ATCC 38626, etc.). Examples of mammalian cells include HEK293 cells derived from human embryonic kidney cells, mouse L929 cells, Chinese hamster ovary (CHO) cells, etc.

Generally, expression vectors are constructed with, at least,

a promoter, an initiation codon, a polynucleotide encoding the amino acid sequence of any of the proteins of the present invention, a termination codon, and a self-replication unit, when prokaryotes, bacteria, particularly E. coli are used as host cells. When eukaryotic cells such as yeast and mammalian cells are used, expression vectors are preferably constructed with, at least, a promoter, an initiation codon, a polynucleotide encoding the amino acid sequence of any of the proteins of the present invention, and a termination codon. Additionally, an enhancer sequence, 5'- and 3'-untranslated regions for the proteins of the present invention, a polyadenylation site, and a self-replication unit may be integrated.

The self-replication unit preferably comprises a selectable marker for transfectants (e.g. resistance to ampicillin). In the case of expression vectors using bacteria as host cells, the term "promoter" means a promoter-operator region containing a promoter, operator, and a Shine-Dalgarno (SD) sequence (e.g. AAGG, etc.). Examples of such promoters include conventional promoter-operator regions (e.g. the lactose operon, PL-promoter, trp-promoter, etc.). An Example of a promoter for expression vectors used in yeast host cells includes the pho5 promoter. Additionally, to facilitate purification, basic amino acids having affinity for chelated metal ions can be added to either end of a protein of the present invention.

When basic amino acids are added, a primer having, at its 5'-end, a nucleotide sequence sequentially coding for desired amino acid residues can be used for PCR to introduce an oligonucleotide at either end of a gene of interest. Histidine, lysine, arginine, and such can be used as basic amino acids.

Examples of promoters used in expression vectors in mammalian cells include the HTLV-LTR promoter, early and late SV40 promoters, CMV promoters, the mouse metallothionein I (MMT) promoter, etc. A preferred example of an initiation codon is the methionine codon (ATG).

A polynucleotide encoding an amino acid sequence of the proteins of the present invention may be obtained by, for example, partial or complete synthesis of nucleotides using a DNA synthesizer. Alternatively, it can be obtained from a human cDNA library by using a probe or primer set that is designed based on a nucleotide sequence

as shown in SEQ ID NO. 1, 3, 5, 7 or 9. The genomic DNA encoding the proteins of the present invention can also be prepared by treating genomic DNA according to a conventional method (e.g. digestion with restriction enzymes, dephosphorylation by bacterial alkaline phosphatase, phosphorylation by T4 polynucleotide kinase, and ligation with T4 DNA ligase). Furthermore, the genomic DNA thus obtained can be used to demonstrate the transcriptional initiation site of a gene of the present invention located on the genome. This allows one to specify expression-regulatory regions located upstream of the gene. Regulatory regions, such as promoters and enhancers, which would control expression of the a encoding a protein of the present invention, are useful as target regions for detecting aberrant expression of a protein of the present invention. Regulation of gene expression can be achieved using decoy nucleotide pharmaceuticals that target such regions.

The host cells of the present invention include cells used for functional analysis of the proteins of the present invention and those used for screening inhibitors or enhancers of the functions of the proteins. Introduction of a vector into host cells may be conducted using any of the methods including, for example, calcium phosphate precipitation, electroporation (Current protocols in Molecular Biology edit. Ausubel et al. (1987) Publish. John Wiley & Sons. Section 9.1-9.9), the lipofectamine method, and microinjection. Preparation of the proteins of the present invention from transfectants may be conducted using any of the isolation and purification methods well known to one skilled in the art.

The present invention also provides a polynucleotide comprising at least 15 nucleotides, which is complementary to any of the polynucleotide sequences shown in SEQ ID NO. 1, 3, 5, 7, or 9, or to a complementary strand thereof. As used herein, the term "complementary strand" refers to one strand of a double-stranded polynucleotide that forms base pairs of A:T (A:U) and G:C with the other strand of the polynucleotide. Also, "complementary" is defined as not only sequences that completely match a continuous nucleotide region of at least 15 nucleotides, but also sequences having a homology of at least 70%, preferably 80% or more, more preferably 90% or more,

and most preferably 95% or more to that region. Sequence homology can be determined according to the algorithm as described in this description.

Such a polynucleotide can be used as a probe for isolating and detecting the DNA or RNA encoding a protein of the invention, or as a primer for amplifying a polynucleotide. When used as a primer, the DNA usually comprises 15-100 bp, and preferably, 15-35 bp. When used as a probe, the DNA comprises the entire sequence of a DNA of the invention, or at least a part of it, and comprises at least 15 bp. When used as a primer, the 3'-region of the polynucletide must be complementary, but the 5'-terminal may contain additional sequences, such as a restriction enzyme recognition site or a tag.

The polynucleotides of the present invention can be used for testing or diagnosing aberrations in the proteins of the present invention. For example, the polynucleotides of the present invention can be used as probes or primers to test aberrations in gene expression by Northern hybridization or RT-PCR. As used herein, the term "expression" includes transcription and/or translation. Expression analysis of the polynucleotides of the present invention may allow the testing and diagnosing of gene expression at the transcriptional level. Gene expression at the translational level may be tested or diagnosed by using antibodies raised against the proteins of the present invention as described below. Polymerase chain reaction (PCR) using as a primer a polynucleotide of the present invention, such as genomic DNA-PCR and RT-PCR, can amplify a polynucleotide encoding a protein of the present invention or an expression regulatory region. Sequence aberrations can be tested or diagnosed using RFLP analysis, SSCP, sequencing, and such.

Moreover, "a polynucleotide comprising at least 15 nucleotides, which is complementary to any of the polynucleotide sequences as set forth in SEQ ID NO. 1, 3, 5, 7 and 9, or to a complementary strand thereof" include antisense polynucleotides for inhibiting the expression of the proteins of the present invention. Antisense polynucleotides comprise at least 15 bp or more, preferably 100 bp or more, more preferably 500 bp or more, and usually 3000 bp or less, preferably 2000 bp or less.

Such antisense polynucleotides are expected to be applied in gene therapy for diseases caused by aberrations (in function or expression) in the proteins of the present invention. Specifically, in Alzheimer's disease, the aggregation and deposition of amyloid-β protein trigger the disease and lead to the cell death of cranial nerve cells and neural dysfunctions . Therefore, if the expression of a protein of the present invention that promotes amyloid-β protein aggregation can be inhibited, it may be useful in the treatment or prevention of Alzheimer's disease. In addition, an Alzheimer's disease model system can be produced if the expression of a protein of the present invention that suppresses amyloid-β protein aggregation can be inhibited, which will result in the promotion of amyloid-β protein aggregation. An antisense polynucleotide can be prepared, for example, by utilizing the phosphorothioate method based on the sequence information of a polynucleotide sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9 ("Physicochemical properties of phosphorothioate oligodeoxynucleotides." Stein (1988) Nucleic Acids Res. 16: 3209-3221).

A polynucleotide or antisense polynucleotide of the present invention can be used in gene therapy, for example, by administrating it to a patient by utilizing the in vivo or ex vivo method using vectors such as retrovirus vectors, adenovirus vectors, and adeno-associating virus vectors, or non-virus vectors such as liposomes.

The present invention also relates to an antibody capable of binding to a protein of the invention. The form of the antibody is not especially restricted; it includes polyclonal antibodies, monoclonal antibodies, or portions thereof, which are capable of binding to an antigen. It also includes antibodies of all classes. Furthermore, specialized antibodies such as humanized antibodies are also included.

If the antibody is a polyclonal antibody, it can be obtained according to the standard method by synthesizing a protein of this invention, or a partial peptide thereof, and immunizing rabbits with the protein or peptide (Current Protocols in Molecular Biology (1987) Ausubel et al. edit, John Wily & Sons, Section 11.12-11.13). If the

antibody is a monoclonal antibody, it can be obtained by immunizing mice with a protein of this invention, or a partial peptide thereof, and producing a hybridoma cell by fusing spleen cells and myeloma cells (Current Protocols in Molecular Biology (1987) Ausubel et al. edit, John Wily & Sons, Section 11.4-11.11).

An antibody capable of binding to a protein of the present invention can be used for purifying a protein of the invention, and also for detecting and/or diagnosing aberrations in the expression and the structure of the protein. Specifically, proteins may be extracted from tissues, blood, or cells, and methods such as western blotting, immunoprecipitation, or ELISA can be used for the above purpose.

Furthermore, an antibody capable of binding to the proteins of the present invention may be utilized for treating diseases associated with the protein. If the antibody is used for treating patients, a human antibody or humanized antibody is desirable in terms of their low antigenicity. Human antibodies can be prepared by immunizing a mouse in which the immune system has been replaced with that of a human ("Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice" Mendez M.J. et al. (1997) Nat. Genet. 15: 146-156, for a reference). Humanized antibodies can be prepared by recombination of the hyper variable region of a monoclonal antibody (Methods in Enzymology (1991) 203: 99-121).

Among the proteins of the present invention, the proteins encoded by the polynucleotides of SEQ ID NOs. 1, 3 and 7 have an inhibitory activity on amyloid-β protein aggregation, and as shown in the Examples below, their expression decreases in patients with Alzheimer's disease. Therefore, augmentation of the expression level of these proteins will prevent amyloid-β protein aggregation, and will be useful for the treatment and prevention of Alzheimer's disease. Additionally, these proteins, and their functional equivalents, can themselves be used as therapeutic and preventive agents for Alzheimer's disease.

Among the proteins of the present invention, the proteins encoded by the polynucleotides of SEQ ID NOs. 5 and 9 have an enhancing activity on amyloid-β protein aggregation, as shown in the working examples

below, and their expression increases in patients with Alzheimer's disease. Therefore, reduction of the expression level of these proteins will prevent amyloid-β protein aggregation, and will be useful for the treatment and prevention of Alzheimer's disease.

Moreover, the proteins of the present invention are expected to relate to other amyloidoses, specifically, schizophrenia and related neuropathies, rheumatoid arthritis, tuberculosis, leprosy, bronchitis, systemic lupus erythematosus (SLE), dialysis amyloidosis, diabetic amyloidosis, atrial amyloidosis, and such, and they can be used as therapeutic and preventive agents for these diseases, or for screening such therapeutic and preventive agents.

The present invention provides a method of screening for compounds regulating the activity of the proteins of the present invention. Since the proteins of the present invention prevent or promote amyloid-β protein aggregation, such compounds may be useful as therapeutic and preventive agents for Alzheimer's disease by regulating the expression of the gene products. This screening is conducted as follows.

A candidate compound that can prevent amyloid-β protein aggregation may be selected by contacting the candidate compound with a protein of the present invention, or cells expressing the protein, under conditions that permit amyloid-β protein aggregation.

More specifically, any of the proteins of the present invention, for example, a protein encoded by the nucleotide sequence of SEQ ID NO. 1, 3, 5, 7 or 9, or a protein functionally equivalent to the protein, or a cell expressing the protein, is incubated with a candidate compound in a solution containing amyloid-β protein (Aβ40, Aβ42, Aβ28, etc.). Subsequently, to determine the degree of aggregation, fluorescence intensity is measured using a fluorescent dye such as thioflavin-T, which binds to, for example, aggregated amyloid-β protein.

Among the proteins of the present invention, the increase of the expression of a protein encoded by a polynucleotide as set forth in SEQ ID NOs. 1, 3 or 7 would inhibit amyloid-β protein aggregation and thus be useful for the treatment and prevention of Alzheimer's disease. . A reduction of the expression of a protein encoded by a polynucleotide as set froth in SEQ ID NOs. 5 or 9 would prevent amyloid-β

protein aggregation, and thus is useful for the treatment and prevention of Alzheimer's disease. Therefore, compounds that can regulate the expression of the genes encoding the proteins of the present invention are useful as therapeutic and preventive agents. Thus, the present invention relates to a method of screening for a compound that can regulate the expression of a protein encoded by a polynucleotide of the present invention, which methodcomprises the following steps of:

(1) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:

an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, and,

a reporter gene operably linked downstream of the expression regulatory region,

(2) measuring the activity of the reporter gene, and,

(3) selecting the candidate compound that increases or decreases the reporter activity measured in step (2) when compared to the control.

To carry out the screening method of the present invention, a regulatory region of the gene is isolated from chromosomal DNA, and an expression plasmid is prepared in which a reporter gene (e.g. luciferase, β-galactosidase, GFP (green fluorescent protein), etc.) is linked downstream of the regulatory region. A regulatory region that controls expression of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9 may be cloned from chromosomal DNA by any method well known in the art. For example, S1 mapping is well known as a method for specifying transcription initiation sites ("Isolation of Transcriptional Regulatory Region" and "Isolation and Purification of Transcription Factors" in Department Oncology, The Institute of Medical Science (ed.), "Current Protocols for Cellular Engineering", Cell Technology, Separate Volume 8, pp. 362-374, Shujunsha Co. Ltd., 1993). In general, screening of a human genomic library using a 15-100bp, preferably 30-50 bp fragment at the 5' terminus of the gene may allow cloning of the DNA for the regulatory region controlling gene expression as a cloned gene comprising the expression regulatory region. The cloned DNA thus obtained often contains 10

kb or longer sequence of the 5'-untranslated region of the gene. Then, the 5'-terminal region of the cloned DNA is shortened or fragmented by treating with, for example, an exonuclease. The minimal unit essential for maintaining the activity of the regulatory region can be found by evaluating the expression level or regulation of expression of the reporter gene using a sequence comprising a shortened expression regulatory region (deletion study). A computer program that predicts expression-regulatory regions of genes using Neural Network is widely known (http://www.fruitfly.org/seq_tools/promoter.html, Reese, M.G., et al, "Large Scale Sequencing Specific Neural Networks for Promoter and Splice Site Recognition" Biocomputing: Proceedings of the 1996 Pacific Symposium, edited by Lawrence Hunter and Terri E. Klein , World Scientific Publishing Co, Singapore, January 2-7, 1996). Alternatively, the minimal unit essential for maintaining the activity is predicted using a program such as the Promoter Scan program that searches for a transcription factor binding sequence and predicts the expression regulatory region (http://biosci.cbs.umn.edu/software/proscan/promoterscan.htm, Prestridge, D.S. 1995, Prediction of Pol II Promoter Sequence using Transcription Factor Binding Sites. J. Mol. Biol. 249: 923-932). The deletion study can be conducted, focusing on the core regions predicted.

An expression plasmid in which a reporter gene is operably linked downstream of the thus isolated gene for the regulatory region is constructed and introduced into an appropriate cell. As used herein, the term "operably linked" means that the two elements are linked so that transcription of the reporter gene is initiated by activation of the above expression regulatory region. Any gene may be used as a reporter gene as long as it encodes a protein that allows one to observe an activation of the above regulatory region as an expression of the gene. Particularly, genes such as luciferase, β-galactosidase, GFP (Green Fluorescent Protein) are typically used as reporter genes. Mammalian cells having a deletion in the corresponding gene, for example, can be used as cells for introducing the vector. Next, mammalian cells having a deletion in the corresponding gene, for example, are transfected with the expression plasmid. Expression of the reporter gene resulting from transcriptional activation by the regulatory

region may be detected as a color development, luminescence, and so on. Under these conditions, this cell strain is seeded into a 96-well multiplate and compounds to be screened are added to each well, thereby allowing easy selection of compounds that can prevent or promote the expression of gene products. As a method for selecting a compound, if GFP is used as the reporter gene, the fluorescence intensities between the presence and absence of the compound can be compared. Comparison refers to when the luminescence ration is two-folds or higher, or 1/2 or lower, preferably five-folds or higher, or 1/5 or lower, and more preferably 10-folds or higher, or 1/10 or lower. This method can be applied to not only animal cells, but also other cells, regardless of being of eukaryotic or prokaryotic origin, as long as they can express a reporter gene in a similar system.

Test samples used in the screening include, for example, cell extracts, expression products of a gene library, synthetic low molecular weight compounds, synthetic peptides, naturally occurring compounds, etc. Note that these test compounds are examples and the present invention is not limited thereto.

Compounds isolated by this screening are candidates for a compound that promotes or suppresses the activity of a protein of the present invention (agonist or antagonist). They are also candidates as compounds that inhibit the interaction between the proteins of the present invention and certain molecules that interact with the proteins. These compounds may be possibly applied to the treatment or prevention of diseases related to the proteins of the present invention.

Further, the present invention relates to use of the compounds obtainable by the screening of the present invention for medical purposes. Thus, the present invention relates to the use of an agent comprising a compound obtainable by the aforementioned screening method as a main ingredient, in the treatment and prevention of Alzheimer's disease, or in the regulation of amyloid β protein aggregation. The present invention also relates to a therapeutic and preventive agent comprising such a compound as a main ingredient. Furthermore, compounds obtained by the screening method of the present invention are expected to be related to other amyloidoses, specifically,

schizophrenia and related neuropathies, rheumatoid arthritis , tuberculosis, leprosy, bronchitis, SLE, dialysis amyloidosis, diabetic amyloidosis, atrial amyloidosis, etc., and can be used as therapeutic and preventive agents for these diseases and for screening such therapeutic and preventive agents.

The proteins, nucleotides, antibodies of the present invention and the compounds isolated by the above screening mentioned are useful for regulating amyloid β protein aggregation. When used as pharmaceutical agents, they themselves can be used as pharmaceutical agents, or they can be formulated for use by any known pharmaceutical method. For example, the compounds can be formulated by mixing with pharmacologically acceptable carriers or vehicles, specifically, sterilized water, physiological saline, plant-oil, emulsifiers, suspending agents, and used. Methods well known to one skilled in the art may be used to administer a pharmaceutical agent to patients, for example as intra-arterial, intravenous, percutaneous injections, and so on. The dosage varies according to the body-weight and age of the patient, and also the administration method, but one skilled in the art can suitably select an appropriate dosage. If the compound can be encoded by a polynucleotide, the polynucleotide can be inserted into a vector for gene therapy to perform the therapy. The dosage and method of administration vary according to the body-weight, age, and symptoms of a patient, but one skilled in the art can select them suitably.

The proteins of the present invention are predicted to have other physiological activities, in addition to the activity of suppressing or promoting amyloid β protein aggregation. Such activities can be determined as follows: Since the proteins of the present invention are secretory or membrane proteins, and their amino acid sequences have been elucidated, it is possible to analyze whether they have other physiological activities, in addition to the activity of suppressing or promoting amyloid β protein aggregation, by expressing recombinants in appropriate expression systems, or by using antibodies that specifically recognize the proteins.

The biological activities of each protein of the present invention can be analyzed, based on, for example, "Glycobiology" M.

Fukuda and A. Kobata (ed.), 1993; "Growth Factors" I. McKay and I. Leigh (ed.), 1993; and "Extracellular Matrix" M. A. Haralson and J. R. Hassell (ed.), 1995; in "The Practical Approach Series", IRL PRESS, or "Glycoprotein Analysis in Biomedicine" Elizabeth F. Hounsell (ed.), 1993; in "Method in Molecular Biology" series, Humana Press. Alternatively, biological activities related to secretory or membrane proteins can be analyzed based on the disclosures found in "Growth and differentiation factors and their receptors", The Japanese Biochemical Society (ed.), Shin-Seikagaku Jikken Kouza Vol.7 , Tokyo-Kagaku-Doujin Co. Ltd, 1991, and in Volume 296 "Neurotransmitter Transporters"; Volume 294 "Ion Channels (Part C)"; Volume 293 "Ion Channels (Part B)", Volume 292 "ABC Transporters"; Volume 288 "Chemokine Receptors"; Volume 287 "Chemokines"; Volume 248 "Proteolytic Enzymes"; Volume 245 "Extracellular Matrix Components"; Volume 244 "Proteolytic Enzymes"; Volume 230 "Guide to Techniques in Glycobiology"; Volume 198 "Peptide Growth Factors"; Volume 192 "Biomembranes"; Volume 191 "Biomembranes"; Volume 149 "Drug and Enzyme Targeting", in "Methods in Enzymology", Academic Press, and so on.

A pharmaceutical agent can be made based on functional analyses using a secretory or membrane protein.

In the case of a membrane protein, it would most likely be a protein having a function as a receptor or ligand by being expressed on the cell surface. Therefore, it is possible to reveal a new ligand-receptor relationship by screening a membrane protein of the invention based on the binding activity with a known ligand or receptor. Screening can be performed according to known methods.

For example, a screening using cells expressing a receptor proteins of the present invention can be performed as follows. Namely, it is possible to screen a receptor capable of binding to a specific protein by using the following steps of: (a) contacting a cell sample with a protein of the invention, or a partial peptide thereof, and (b) selecting a cell that binds to the protein or peptide.

This screening can be conducted, for example, as follows. First, a protein of the invention is expressed, and the recombinant protein is purified. Next, the purified protein is labeled, binding assay is performed using various cell lines or primary cultured cells,

and cells that are expressing a receptor are selected (Growth and differentiation factors and their receptors, Shin-Seikagaku Jikken Kouza Vol.7 (1991) Honjyo, Arai, Taniguchi, and Muramatsu edit, p203-236, Tokyo-Kagaku-Doujin). Protein labeling can be achieved by labeling with radioisotopes (RI) such as ^{125}I, and by enzymes (alkaline phosphatase etc.) as well. Alternatively, a protein of the invention may be used without labeling, and then detected by using a labeled antibody against the protein. The cells that are selected by the above screening methods, which express a receptor of a protein of the invention, can be used for further screening agonists or antagonists of the receptor.

Once a receptor of a protein of the invention or the cells expressing the receptor is obtained by screening, it is possible to screen a compound that inhibits the binding between the protein and its receptor (agonists or antagonists of the receptor, for example) by utilizing the binding ability of the protein to its receptor or cells expressing the receptor.

The screening method comprises the steps of : (a) contacting a protein of the invention with its receptor or cells expressing the receptor in the presence of a test sample, (b) detecting the binding activity between the protein and its receptor or the cells expressing the receptor, and (c) selecting a compound that can reduce the binding activity compared to the activity in the absence of the sample.

Test samples that can be used in the screening include cell extracts, expression products of a gene library, synthesized low molecular compounds, synthesized peptides, and natural compounds, for example, but are not limited thereto. A compound that is isolated by the above screening using the binding ability of a protein of the invention can be also used as the test sample.

A compound isolated by the screening may be a candidate for an agonist or an antagonist of a receptor of a protein of the invention. By utilizing an assay that monitors a change in intracellular signaling such as phosphorylation, which results from the reduction of the binding between the protein and its receptor, it is possible to identify whether the obtained compound is an agonist or antagonist of the

receptor. Also, the compound may be a candidate for a molecule that can inhibit the interaction between a protein of the invention and its associating proteins (including receptors). Such compounds can be used for developing drugs for preventing or treating a disease associated with the protein of the invention.

When a protein of the invention is a secretory protein, it may be a factor that can regulate cellular conditions such as growth and differentiation. A novel factor that regulates cellular conditions can be discovered by adding the secretory protein of the invention to a certain kind of cell, and performing screening by utilizing a cellular change in growth or differentiation, or activation of a particular gene.

The screening may be performed, for example, as follows. First, the protein of the invention is expressed and the recombinant protein is purified. Then, the purified protein is added to various kinds of cell lines or primary cultures, and a change in the cell growth and/or differentiation is monitored. Alternatively, the induction of a particular gene that is known to be involved in a certain cellular change can be detected at the level of mRNA expression or protein amount. Alternatively, the amount of an intracellular molecule (low molecular compounds) that is changed by the function of a gene product (protein) that is known to be functioning in a certain cellular change may be used for the detection.

Once the screening reveals that a protein of the invention can regulate cellular conditions or functions, it is possible to apply the protein as a pharmaceutical agent for related diseases by itself or by altering a part of it.

As was described for membrane proteins, secretory proteins provided by the invention may be used to explore a novel ligand-receptor interaction using a screening based on the binding ability to a known ligand or receptor. A similar method can be used to identify an agonist or antagonist. The resulting compounds obtained by the methods can be candidates for compounds that can inhibit the interaction between a protein of the invention and an interacting molecule (including receptors). Such compounds may used as pharmaceutical agents for preventing and treating diseases, in which the protein may play a

certain role.

If a protein or gene that is affected by the screening turns out to be associated with a disease, it is possible to screen a gene or compound that can regulate its expression and/or activity either directly or indirectly by utilizing a protein of the present invention.

For example, a protein of the invention is expressed and purified as a recombinant protein. Then, the protein or gene that is affected by the screening is purified, and screened by the binding ability. Alternatively, the screening can be performed by adding in advance a compound that is a candidate for an inhibitor, and observing changes in binding. Compounds obtained by such a screening can be used for developing pharmaceutical agents for diseases with which a proteins of the present invention is associated. Similarly, if a regulatory factor obtained by the screening turns out to be a protein, a compound that affects the original expression level and/or activity of the protein can be used for the same purpose described above.

If a secretory or membrane proteins of the present invention has an enzymatic activity, it is possible to identify the activity by adding a compound to the protein under appropriate conditions, and monitoring a change of the compound. It is also possible to screen a compound that inhibits an activity of a protein of the invention by utilizing the activity as an index.

In a screening given as an example, a protein of the invention is expressed and the recombinant protein is purified. Then, a compound is added to the purified protein, and the amount of the compound and the reaction products are examined. Alternatively, a compound that is a candidate for an inhibitor is pretreated, then the compound (substrate) that can react with the purified protein is added, and the amount of the substrate and the reaction products are examined.

The compounds obtained in the screening may be used as pharmaceutical agents for diseases with which a protein of the invention is associated.

Whether or not the secretory or membrane proteins of the present invention is a novel protein associated with a disease is determined using also methods other than those described above. Namely, this

can be done by obtaining a specific antibody against a protein of the invention, and examining the relationship between the expression or activity of the protein and a certain disease. In an alternative way, it may be analyzed referring to methods in "Molecular Diagnosis of Genetic Diseases" (Elles R. edit, (1996) in the series of "Method in Molecular Biology" (Humana Press).

In addition to purifying a protein of the invention, an antibody that binds to a protein of the invention may be used , for example, for testing or diagnosing structural or functional aberrations of the protein of the present invention .

Polynucleotides of the present invention were observed to be aberrantly expressed in the hippocampus of patients with Alzheimer's disease. Therefore, Alzheimer's disease may be detected by measuring the expression of a polynucleotide of the present invention. Thus, the present invention relates to a method for detecting Alzheimer's disease, comprising the following steps of:

(1) measuring the expression of at least one of the polynucleotides selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 3, SEQ ID NO. 7, and SEQ ID NO. 9,

(2) comparing the measurement obtained with that obtained when the polynucleotide is expressed in healthy subjects; and,

(3) linking Alzheimer's disease with said change in expression of the polynucleotide.

In the present invention, an expression state of a polynucleotide can be understood by analyzing any one of the steps in the transcription of the gene into mRNA and in the translation into the protein. More specifically, the state of transcription can be understood by measuring mRNA comprising an aforementioned nucleotide sequence in place of an aforementioned polynucleotide. Any known method, such as Northern hybridization and RT-PCR, can be used to measure mRNA. Alternatively, measurement of a protein having an amino acid sequence encoded by a polynucleotide, or a fragment of the protein, would elucidate the state of translation into the protein. Proteins can be measured by Western blot using antibodies recognizing the proteins and various immunoassays. The testing method of the present invention can be conducted for blood samples and spinal fluid samples, or hippocampal

tissue obtained by an autopsy. To observe the state of expression of the polynucleotides of the present invention, using tissue specimens as samples, analytical methods, such as *in situ* hybridization and immunohistological techniques, may be used. if the state of expression of a polynucleotide of the present invention is analyzed, and if, for example, the expression of PSEC256 is found to be enhanced in the brain of AD patients compared to the expression in normal brains, PSEC256 can be linked to Alzheimer's disease. Also, if inhibition of the expression of PSEC0012, PSEC0220, PSEC0242, or such, is observed, they can also be linked to Alzheimer's disease.

The present invention also relates to a reagent for revealing an expression state of a polynucleotide of the present invention. More specifically, the present invention relates to the use of a polynucleotide comprising at least 15 nucleotides, which is complementary to any one of the polynucleotides of the present invention, or to a complementary strand thereof, for detecting a polynucleotide of the present invention. Alternatively, the present invention relates to the use of an antibody recognizing any one of the proteins of the present invention for detecting the protein.

Best Mode for Implementing the Invention

The present invention shall be described in detail below with reference to examples, but it is not be construed as being limited thereto.

Example 1: Cloning of cDNAs that encode the proteins promoting or preventing aggregation and deposition of amyloid β protein

NT-2 neuron progenitor cells (Stratagene), a teratocarcinoma cell line from human embryo testis, which can differentiate into neurons when treated with retinoic acid, were used. The NT-2 cells were cultured according to the manufacturer's instructions,

(1) without retinoic acid treatment (NT2RM1),

(3) 2 weeks after retinoic acid was added to cultured NT-2 cells (NT2RP3)

The cells were harvested separately, from which mRNA was extracted by the method described in the literature (Molecular Cloning 2nd edition. Sambrook J., Fritsch, E.F., and Maniatis T. (1989) Cold

Spring Harbor Laboratory Press). Poly(A)$^+$RNA was further purified from the mRNA using oligo-dT cellulose.

Similarly, human placenta (PLACE1), and brain-enriched tissues from human embryo (HEMBA1) were used to extract mRNA by the method described in the literature (Molecular Cloning 2nd edition. Sambrook J., Fritsch, E.F., and Maniatis T. (1989) Cold Spring Harbor Laboratory Press). Poly(A)$^+$RNA was further purified from the mRNA using oligo-dT cellulose.

Each poly(A)$^+$RNA was used to construct a cDNA library by the oligo-capping method (Maruyama M. and Sugano S. (1994) Gene 138: 171-174). Using the Oligo-cap linker (agcaucgagu cggccuuguu ggccuacugg/SEQ ID NO: 11) and the Oligo-dT primer (gcggctgaag acggcctatg tggccttttt ttttttttt tt/SEQ ID NO: 12), BAP (Bacterial Alkaline Phosphatase) treatment, TAP (Tobacco Acid Phosphatase) treatment, RNA ligation, the first strand cDNA synthesis, and removal of RNA were performed as described in the reference (Suzuki and Kanno (1996) Protein Nucleic acid and Enzyme. 41: 197-201; Suzuki Y. et al. (1997) Gene 200: 149-156). Next, 5'- and 3'-PCR primers ((agcatcgagt cggccttgtt g/SEQ ID NO: 13) and (gcggctgaag acggcctatg t/SEQ ID NO: 14) respectively) were used to perform PCR (polymerase chain reaction) to convert the cDNA into double stranded cDNA, which was then digested with SfiI. Then, the DraIII-cut pUC19FL3 vector (for NT2RM1), or pME18SFL3 (GenBank AB009864, expression vector; for NT2RP3, PLACE1, and HEMBA1) was used for cloning the cDNA in an unidirectional manner, and cDNA libraries were obtained. The clones having an insert cDNA of 1 kb length or shorter were removed for NT2RM1, PLACE1, and HEMBA1, and the clones having an insert of 2 kb or shorter were removed for NT2RP3. Then, the nucleotide sequence of the 5'- and 3'- ends of the cDNA clones was analyzed using DNA sequencing reagents (Dye Terminator Cycle Sequencing FS Ready Reaction Kit, dRhodamine Terminator Cycle Sequencing FS Ready Reaction Kit, or BigDye Terminator Cycle Sequencing FS Ready Reaction Kit, from by PE Biosystems), performing sequencing reactions according to the instructions, and analyzing with a DNA sequencer (ABI PRISM 377, PE Biosystems).

The pME18SFL3 eukaryotic expression vector was used for the

construction of the cDNA libraries, except for NT2RM1. The vector contains SRα promoter and SV40 small t intron in the upstream of the cloning site, and SV40 polyA added signal sequence site in the downstream. As the cloning site has asymmetrical DraIII sites, and cDNA fragments contain a complementary SfiI site on their ends, the cloned cDNA fragments can be inserted downstream of the SRα promoter unidirectionally. Therefore, the plasmid clones containing full-length cDNA can be introduced directly into COS cells to be expressed transiently. Thus, experimental analysis as proteins (gene products) or as biological activities can be very easily carried out.

The fullness ratio of the 5'-end sequence of the cDNA clones in the libraries constructed by the oligo-capping method was determined as follows. For all the clones in which the 5'-end sequence was identical to that of any known human mRNA in the public database, the clones were judged to be "complete/full length", if they had a longer 5'-end sequences than the known human mRNA, or, even if the 5'-end sequence was shorter, if they contained a translation initiation codon. A clone that did not contain a translation initiation codon was judged to be "incomplete/not full length". The fullness ratio ((the number of complete clones)/(the number of complete clones) + (the number of incomplete clones)) of the 5'-end of the cDNA clones from each library was determined by comparing with the known human mRNA (NT2RM1: 69%; NT2RP3: 61%; PLACE1: 68%; HEMBA1: 53%). The result indicates that the fullness ratio of the 5'-end sequence was extremely high.

The relationship between the cDNA libraries and the clones is shown below.

HEMBA1: PSEC0220

NT2RM1: PSEC0012

NT2RP3: PSEC0242, PSEC0256

PLACE1: PSEC0129

Furthermore the complete cDNA sequence and the predicted amino acid sequence of the clones thus selected were determined. The final nucleotide sequences were determined by combining the following three methods, and overlapping the nucleotide sequences determined by each

method.

(1) Long read sequencing from both ends of the cDNA inserts using a Licor DNA sequencer (Sequence reactions were performed according to the manual of the Licor sequencer (Aloka), and DNA sequence was determined using the sequencer.)

(2) Nested sequencing by the Primer Island method which utilizes the in vitro integration reaction of AT2 transposon (Devine S.E., and Boeke J.D. (1994) Nucleic Acids Res. 22: 3765-3772) (Clones were obtained using a kit from PE Biosystems, and sequence reactions were performed using the DNA sequencing reagents from the same company, according to the manufacturer's instructions, and DNA sequence was determined using an ABI PRISM 377 sequencer).

(3) Primer walking by the dideoxy terminator method using custom synthesized DNA primers (Sequencing reactions were performed using the DNA sequencing reagents from PE Biosystems and custom synthesized DNA primers according to the manufacturer's instructions. DNA sequence was determined using an ABI PRISM 377 sequencer).

Obtained sequences were subjected to analysis by ATGpr [A. A. Salamov, T. NISHIKAWA, M. B. Swindells, Bioinformatics, 14: 384-390 (1998); http://www.hri.co.jp/atgpr/] and PSORT, and also to BLAST search of GenBank and SwissProt. As a result, most clones were predicted to be secretory or membrane proteins that contain a signal sequence at the N-terminus. For PSEC0242 and PSEC0256, no signal sequence was detected, but the presence of a transmembrane helix was identified by SOSUI, predicting that they are membrane proteins. The results of the above analyses suggest that PSEC0012, PSEC0129, and PSEC0220 are secretory or membrane proteins and have signal sequences at their N-termini, which indicates that they are full-length cDNA clones. PSEC0242 and PSEC0256 are membrane proteins and are predicted to be full-length cDNA clones, although they lack a signal sequence. For PSEC242, a signal sequence could be found at the N-terminus, if the translation is initiated from the third ATG.

PSEC0242: No.3 ATG, ATGpr1 0.82, SP-Yes, ORF 171-1343 391 aa, Signal peptide 24;

These results are shown below. The data are shown in the following order, subsequent to each clone name. Each data is discriminated by

"//".
Clone name//
Size of cDNA//
Number of amino acid residues composing the predicted amino acid sequence//
Number of ATG counted from the N-terminus//
Maximal ATGpr1 value//
Presence or absence of signal sequences, or prediction of signal sequence by PSORT, prediction of membrane proteins by MEMSTAT and SOSUI//
Annotation:
PSEC0012//C-NT2RM1000853//1499//183//1//0.82//125/183 (68.3%) aa identity to fugu putative protein 2 (PUT2).
PSEC0129//C-PLACE1004170//1828//135//1//0.94//1564/1615 (96%) similarity to human chromosome 16q13/21 BAC clone CIT987SK-A-152E5
PSEC0220//C-HEMBA1005301//1584//365//1//0.94//354/365 (96%) aa identity to mouse WNT-6 protein precursor; 1084/1310 (82%) similarity to mouse Wnt-6 mRNA
PSEC0242//C-NT2RP3000266//3017//401//1//0.90//No & transmembrane//242/242 (100%) similarity to human Newcastle disease virus inducible protein mRNA, partial 3' UTR region; 85/341 (24%) aa identity to human myosin heavy chain.
PSEC0256//C-NT2RP3003549//3520//612//1//0.89//No & transmembrane//97/362 (26%) aa identity to rat cadherin-6 precursor; 1174/1394 (84%) similarity to mRNA for KIAA0345.

Example 5: Expression of the proteins promoting or preventing amyloid β protein aggregation

COS cells (6×10^6 cells/dish) were seeded, and the expression plasmids (10 μg) obtained in Example 1 were added together with 10 μl of LIPOFECTAMINE (Gibco BRL) to transfect the COS7 cells. The recombinant cells thus created, which expressed the gene of interest were cultured in D-MEM medium (+10% FCS, Pc. Sm.) for three days. Supernatant of the cultured medium was collected as a supernatant fraction.

Example 6: Amyloid β aggregation reaction

The supernatants obtained in Example 5 were used to screen for proteins that promote or suppress amyloid β protein aggregation. In principle, the experiments were conducted according to Methods in Enzymology Volume 309 (1999) p 274-284. Instead of Aβ40 and Aβ42, which are commonly found in vivo, Aβ1-28 consisting of 28 amino acid residues from the N-terminus of Aβ, which is considered to aggregate to a similar extent as Aβ40 and Aβ42, was used in the experiments. Experiments as shown below were conducted, and as a result, five clones showing augmented promotion or suppression of aggregation were selected from 108 clones. Experiment method and the activities of the five selected clones are shown below.

(Experiment method)

Three microliters of 1 mM Aβ1-28 (Bachem) was added to 17 μl of the culture supernatant obtained in Example 2, and the reaction was initiated by adding 10 μl of 300 mM sodium acetate buffer (pH 5.2). After 24 hours, 200 μl of 10 μM thioflavin-T (in 50mM potassium phosphate) was added to 5 μl of the reaction sample. Aβ aggregation was determined by measuring the fluorescence intensity (excitation 450 nm、emission 482 nm). Synthesized Aβ40-1 (a peptide having the inverse sequence of Aβ40) was added to the control to a concentration of 100 μM, instead of adding the culture supernatant. The results are shown in the table below. In the table, relative fluorescence intensities are shown, when the fluorescence intensity of the Aβ1-28 aggregation resulting from the addition of Aβ40-1 is taken to be 100%.

Table. 1 Changes of fluorescence intensity due to Aβ1-28 aggregates resulting from addition of Aβ40-1

Protein	Fluorescence Intensity
PSEC0012 (supernatant containing product expressed from the clone of SEQ ID NO: 1)	24%
PSEC0129 (supernatant containing the product expressed from the clone of SEQ ID NO: 3)	24%
PSEC0220 (supernatant containing the product expressed from the clone of SEQ	250%

ID NO. 5)	
PSEC0242 (supernatant containing the product expressed from the clone of SEQ ID NO. 7)	16%
PSEC0256 (supernatant containing the product expressed from the clone of SEQ ID NO. 9)	460%

The proteins expressed from the clones comprising the polynucleotides of SEQ ID NOs: 1, 3 and 7 in the sequence list prevent aggregation of amyloid β protein, and the proteins expressed from the clones comprising the polynucleotides of SEQ ID NOs: 5 and 9 in the sequence list promote aggregation of amyloid β protein.

Furthermore, deposition of aggregated synthetic Aβ was confirmed through microscopic observation after staining with Congo red.

Example 6: Gene Expression analysis in patients with Alzheimer's disease

Expression levels of the gene were compared between healthy subjects and patients with Alzheimer's disease. The primers shown below were prepared for each clone, and quantitative PCR was conducted using hippocampal cDNA as template. Hippocampal cDNA from an Alzheimer's disease patient (age 60) (NO. 0550903) and one from a healthy subject (age 28) (NO. 0510069) were purchased from BioChain Institute Inc. and used. Analysis of the expression levels was performed using PE Applied Biosystems PRISM 7700 according to the protocol for quantitative PCR using SYBR Green (P/N 4304965). The four sets of primers used for PCR are as follows:

PSEC012-894F: GTGGATGCGATCTGTCTCTCC (SEQ ID NO. 15)
PSEC012-1049R: TGCAGAAAGGAACACATGCTG (SEQ ID NO. 16)
PSEC129-190F: CTTCCATGCTTCAGCTGTGG (SEQ ID NO. 17)
PSEC129-340R: GCCCTGGTCTGTATACCTGGG (SEQ ID NO. 18)
PSEC242-599F: CTACGACCTGAGCCAGTGCA (SEQ ID NO. 19)
PSEC242-749R: GAGGGCTTGGAGCTGCTGT (SEQ ID NO. 20)
PSEC256-1502F: GCATTCTACGGGCTGGTCC (SEQ ID NO. 21)
PSEC256-1652R: GGGTTGCCTGGTCCGTATT (SEQ ID NO. 22)

The expression level was reduced in the Alzheimer's disease

patient, compared to the healthy subject, to 1/2 for PSEC012, 1/10 for PSEC129, and 1/9 for PSEC242. On the contrary, the expression level of PSEC256 was increased 1.5 folds in the Alzheimer's disease patient.

Industrial Applicability

The present invention provides proteins that suppress or promote aggregation and deposition of amyloid-β protein, and polynucleotides encoding the proteins. The proteins of the present invention and the polynucleotides encoding the proteins are useful as pharmaceutical agents for treating and preventing diseases including Alzheimer's disease, and for diagnosing these diseases. Also, the present invention has enabled screening for a compound that suppresses or promotes aggregation of amyloid-β protein. It is hoped that the screening method of the present invention would be used for developing effective therapeutic agents for Alzheimer's disease that prevent amyloid-β aggregation.

CLAIM

1. A polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid-β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9.

2. A polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide according to claim 1.

3. A peptide or protein encoded by a polynucleotide according to claim 1 or 2.

4. A protein that suppresses or promotes the aggregation of amyloid-β protein, wherein said protein is encoded by a polynucleotide that, from a molecular evolutionary aspect, originated from the same gene from which a polynucleotide according to claim 1 originated from.

5. A vector comprising a polynucleotide according to claim 1 or 2.

6. A transfectant harboring a polynucleotide according to claim 1 or 2 or the vector according to claim 5.

7. A method for producing the peptide or protein according to claim 3, wherein said method comprises the steps of: culturing the transfectant according to claim 6, and recovering the expression product.

8. A polynucleotide comprising a polynucleotide according to claim 1 or 2 or a nucleotide sequence complementary to the complementary

strand of a polynucleotide according to claim 1 or 2, wherein said polynucleotide comprises at least 15 nucleotides.

9. An antibody against the peptide or protein according to claim 3.

10. An immunological assay comprising the step of: monitoring an immunological reaction between the peptide or protein according to claim 3 and the antibody according to claim 9.

11. A method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to claim 1, wherein said method comprises the following steps of:

contacting a candidate compound with a protein encoded by a polynucleotide according to claim 1, or with a cell expressing said protein, in the presence of amyloid-β protein, and,

selecting a the candidate compound that regulates the aggregation or deposition of amyloid-β protein.

12. A method of screening for a compound that regulates expression of a protein encoded by a polynucleotide according to claim 1, wherein said method comprises the following steps of:

(1) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:

an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and,

a reporter gene operably linked downstream of the expression regulatory region,

(2) measuring the activity of the reporter gene, and,

(3) selecting the candidate compound that increases or decreases the reporter activity measured in step (b) when compared to the control.

13. A pharmaceutical agent comprising a compound obtained by the method according to claim 11 or 12.

14. A pharmaceutical agent comprising the peptide or protein according to claim 3 or 4.

15. A pharmaceutical agent comprising an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to claim 1.

16. The pharmaceutical agent according to claim 13 or 14, wherein said pharmaceutical agent is a preventive or therapeutic agent for Alzheimer's disease, and,

17. A method for detecting Alzheimer's disease, comprising the following steps of:

(1) measuring the expression of a polynucleotide according to claim 1,

(2) comparing the measurement obtained by (1) with that obtained when the polynucleotide is expressed in healthy subjects,

(3) linking Alzheimer's disease with said change in expression of the polynucleotide.

ABSTRACT

The present invention provides: proteins suppressing or promoting the aggregation or deposition of amyloid-β protein; polynucleotides encoding the proteins; a method for screening a compound suppressing or promoting the aggregation or deposition of amyloid-β protein; and therapeutic agents for treating or preventing Alzheimer's diseases comprising a compound that regulates the activity of a protein suppressing or promoting the aggregation or deposition of amyloid-β protein.

Japanese Language Declaration
(日本語宣言書)

第三の共同発明者の氏名	Full name of third joint inventor, If any Tetsuo NISHIKAWA
第三の共同発明者の署名　日付	Third inventor's signature　Date
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, Tokyo 173-0013, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of fourth joint inventor, If any Yuri HIO
第四の共同発明者の署名　日付 3-00	Fourth inventor's signature　Date Yuri Hio　May 30, 2002
住所	Residence 4508-19-201, Yana, Kisarazu-shi, Chiba JPX 292-0812, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第五の共同発明者の氏名	Full name of fifth joint inventor, If any Mayako YAMAZAKI
第五の共同発明者の署名　日付	Fifth inventor's signature　Date
住所	Residence 11-9, Hongo 2-chome, Toride-shi, Ibaraki 302-0022, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

217925US0XPCT

Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

As a below named inventor, I hereby declare that:

私の住所、郵便の宛先、国籍は下記の私の氏名の後に記載された通りです。

My residence, mailing address and citizenship are as stated next to my name.

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

AMYLOID-β PROTEIN AGGREGATION-REGULATING FACTORS (as amended)

上記発明の明細書は、

the specification of which

☐ 本書に添付されています。

☐ is attached hereto.

☐ _____ 月 _____ 日に提出され、米国出願番号または特許協定条約国際出願番号を

_____ とし、

(該当する場合) _____ に訂正されました。

☒ was filed on July 6, 2000

as United States Application Number or PCT International Application Number

PCT/JP00/04515 and was amended on

_____ (if applicable)

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は、連邦規則法典第37編第1条56項に定義されるとおり、特許資格の有無について重要な情報を開示する義務があることを認めます。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Japanese Language Declaration
(日本語宣言書)

私は、米国法典第 35 編 119 条(a) – (d)項又は 365 条 (b)項
に基づき下記の、米国以外の国の少なくとも一ヵ国を指定している特許協力条約 365(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

I hereby claim foreign priority under Title 35, United States Code, § 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)
外国での先行出願

(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	Priority Claimed 優先権主張 Yes はい	No いいえ
11/194179	Japan	8 July 1999	☒	☐

私は、第 35 編米国法典 119 条 (e) 項に基づいて下記の米国特許出願規定に記載された権利をここに主張いたします。

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)
60/159,586	18 October 1999

私は、下記の米国法典第 35 編 120 条に基づいて下記の米国特許出願に記載された権利、又は米国を指定している特許協力条約 365 条 (c) に基づく権利をここに主張します。また、
本出願の各請求範囲の内容が米国法典第 35 編 112 条第 1 項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内または特許協力条約国際提出日までの期間中に入手された、連邦規則法典第 37 編 1 条 56 項で定義さ
れた特許資格の有無に関する重要な情報について開示義務があることを認識しています。

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)
PCT/JP00/04515	6 July 2000	Pending

私は、私自身の知識に基づいて本宣言書中で私が行なう表明が真実であり、かつ私の入手した情報と私の信じるところに基づく表明が全て真実であると信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第 18 編第 1001 条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行なえば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration
(日本語宣言書)

委任状：私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。
（弁護士、または代理人の指名及び登録番号を明記のこと）

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)

022850

書類送付先

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単独発明者または第一の共同発明者の氏名	Full name of sole or first inventor Toshio OTA
発明者の署名　日付	Inventor's signature　Date
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国籍	Citizenship Japan
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第二の共同発明者の氏名	Full name of second joint inventor, If any Takao ISOGAI
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Japanese Language Declaration
(日本語宣言書)

第六の共同発明者の氏名 5-00	Full name of sixth joint inventor, If any Susumu SATOH
第六の共同発明者の署名 日付	Sixth inventor's signature Date Susumu Satoh April 12, 2002
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住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

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第三の共同発明者の署名 日付	Seventh inventor's signature Date Hiroyuki Arakawa April 12, 2002
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住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

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第四の共同発明者の署名 日付	Eighth inventor's signature Date M Morita Apr 17.'02
住所	Residence 1-20-1-2-103, Chuo, Ushiku-shi, Ibaraki 300-1234, JPX Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

Japanese Language Declaration
(日本語宣言書)

第六の共同発明者の氏名	Full name of sixth joint inventor, If any Susumu SATOH
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第四の共同発明者の署名　日付	Eighth inventor's signature　Date
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217925US0XPCT

Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

私の住所、郵便の宛先、国籍は下記の私の氏名の後に記載された通りです。

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

上記発明の明細書は、

☐ 本書に添付されています。

☐ _____ 月 _____ 日に提出され、米国出願番号または特許協定条約国際出願番号を

_____ とし、

（該当する場合） _____ に訂正されました。

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I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

AMYLOID-β PROTEIN AGGREGATION-REGULATING FACTORS (as amended)

the specification of which

☐ is attached hereto.

☒ was filed on July 6, 2000

as United States Application Number or PCT International Application Number

PCT/JP00/04515 and was amended on

_____ (if applicable)

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I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

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(日本語宣言書)

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に基づき下記の、米国以外の国の少なくとも一ヵ国を指定している特許協力条約 365(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

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Prior Foreign Application(s)
外国での先行出願

(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	Priority Claimed 優先権主張 Yes はい	 No いいえ
11/194179	Japan	8 July 1999	☒	☐

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I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)
60/159,586	18 October 1999

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本出願の各請求範囲の内容が米国法典第 35 編 112 条第 1 項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内または特許協力条約国際提出日までの期間中に入手された、連邦規則法典第 37 編 1 条 56 項で定義さ
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(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)
PCT/JP00/04515	6 July 2000	Pending

私は、私自身の知識に基づいて本宣言書中で私が行なう表明が真実であり、かつ私の入手した情報と私の信じるところに基づく表明が全て真実であると信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第 18 編第 1001 条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行なえば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration
(日本語宣言書)

委任状：私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。
（弁護士、または代理人の指名及び登録番号を明記のこと）

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)

022850

書類送付先

Send Correspondence to:

022850

直接電話連絡先：（名前及び電話番号）

Direct Telephone calls to: (name and telephone number)

(703) 413-3000

単独発明者または第一の共同発明者の氏名 1-00	Full name of sole or first inventor Toshio OTA
発明者の署名 日付	Inventor's signature Date Toshio Ota June 10, 2002
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国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

第二の共同発明者の氏名	Full name of second joint inventor, If any Takao ISOGAI
第二の共同発明者の署名 日付	Second inventor's signature Date
住所	Residence 511-12, Omuro, Ami-machi, Inashiki-gun, Ibaraki 300-0303, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

(6)

Japanese Language Declaration
(日本語宣言書)

第三の共同発明者の氏名	Full name of third joint inventor, If any Tetsuo NISHIKAWA
第三の共同発明者の署名　日付	Third inventor's signature　Date
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, Tokyo 173-0013, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of fourth joint inventor, If any Yuri HIO
第四の共同発明者の署名　日付	Fourth inventor's signature　Date
住所	Residence 4508-19-201, Yana, Kisarazu-shi, Chiba 292-0812, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第五の共同発明者の氏名	Full name of fifth joint inventor, If any Mayako YAMAZAKI
第五の共同発明者の署名　日付 4-00	Fifth inventor's signature　Date Mayako Yamazaki　April 17, 2002
住所	Residence 11-9, Hongo 2-chome, Toride-shi, Ibaraki 302-0022, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

Japanese Language Declaration
(日本語宣言書)

第三の共同発明者の氏名	Full name of third joint inventor, If any Tetsuo NISHIKAWA
第三の共同発明者の署名　日付	Third inventor's signature　Date
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, Tokyo 173-0013, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

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住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第五の共同発明者の氏名	Full name of fifth joint inventor, If any Mayako YAMAZAKI
第五の共同発明者の署名　日付	Fifth inventor's signature　Date
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住所	Citizenship Japan
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Japanese Language Declaration
(日本語宣言書)

第六の共同発明者の氏名	Full name of sixth joint inventor, If any Susumu SATOH
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第四の共同発明者の氏名	Full name of eighth joint inventor, If any Masahiko MORITA
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住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

217925US0XPCT

Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

私の住所、郵便の宛先、国籍は下記の私の氏名の後に記載された通りです。

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

上記発明の明細書は、

☐ 本書に添付されています。

☐ _____ 月 _____ 日に提出され、米国出願番号または特許協定条約国際出願番号を

_____ とし、

（該当する場合） _____ に訂正されました。

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

私は、連邦規則法典第 37 編第 1 条 56 項に定義されるとおり、特許資格の有無について重要な情報を開示する義務があることを認めます。

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

AMYLOID-β PROTEIN AGGREGATION-REGULATING FACTORS (as amended)

the specification of which

☐ is attached hereto.

☒ was filed on July 6, 2000

as United States Application Number or PCT International Application Number

PCT/JP00/04515 and was amended on

_____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Japanese Language Declaration
(日本語宣言書)

私は、米国法典第 35 編 119 条(a) – (d)項又は 365 条 (b)項
に基づき下記の、米国以外の国の少なくとも一ヵ国を指定している特許協力条約 365(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

I hereby claim foreign priority under Title 35, United States Code, § 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s) 外国での先行出願			Priority Claimed 優先権主張	
11/194179	Japan	8 July 1999	☒	☐
(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	Yes はい	No いいえ

私は、第 35 編米国法典 119 条 (e) 項に基づいて下記の米国特許出願規定に記載された権利をここに主張いたします。

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)	60/159,586 (Application No.) (出願番号)	18 October 1999 (Filing Date) (出願日)

私は、下記の米国法典第 35 編 120 条に基づいて下記の米国特許出願に記載された権利、又は米国を指定している特許協力条約 365 条 (c) に基づく権利をここに主張します。また、
本出願の各請求範囲の内容が米国法典第 35 編 112 条第 1 項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内または特許協力条約国際提出日までの期間中に入手された、連邦規則法典第 37 編 1 条 56 項で定義さ
れた特許資格の有無に関する重要な情報について開示義務があることを認識しています。

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PCT/JP00/04515 (Application No.) (出願番号)	6 July 2000 (Filing Date) (出願日)	Pending (Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)
(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)

私は、私自身の知識に基づいて本宣言書中で私が行なう表明が真実であり、かつ私の入手した情報と私の信じるところに基づく表明が全て真実であると信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第 18 編第 1001 条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行なえば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration
(日本語宣言書)

委任状：私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。
（弁護士、または代理人の指名及び登録番号を明記のこと）

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)

022850

書類送付先

Send Correspondence to:

022850

直接電話連絡先：（名前及び電話番号）

Direct Telephone calls to: (name and telephone number)

(703) 413-3000

単独発明者または第一の共同発明者の氏名	Full name of sole or first inventor Toshio OTA
発明者の署名　日付	Inventor's signature　Date
住所	Residence c/o Kyowa Hakko Kogyo Co., Ltd., Tokyo Research Laboratories, 3-6-6, Asahi-machi, Machida-shi, Tokyo 194-8533, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

第二の共同発明者の氏名 2-00	Full name of second joint inventor, If any Takao ISOGAI
第二の共同発明者の署名　日付	Second inventor's signature　Date Takao Isogai　June 11, 2002
住所	Residence 511-12, Omuro, Ami-machi, Inashiki-gun, Ibaraki JPX 300-0303, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

Japanese Language Declaration
(日本語宣言書)

第三の共同発明者の氏名	Full name of third joint inventor, If any Tetsuo NISHIKAWA
第三の共同発明者の署名 日付 3-00	Third inventor's signature Date Tetsuo Nishikawa June 11, 2002
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, Tokyo JPX 173-0013, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of fourth joint inventor, If any Yuri HIO
第四の共同発明者の署名 日付	Fourth inventor's signature Date
住所	Residence 4508-19-201, Yana, Kisarazu-shi, Chiba 292-0812, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第五の共同発明者の氏名	Full name of fifth joint inventor, If any Mayako YAMAZAKI
第五の共同発明者の署名 日付	Fifth inventor's signature Date
住所	Residence 11-9, Hongo 2-chome, Toride-shi, Ibaraki 302-0022, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

Japanese Language Declaration
(日本語宣言書)

第六の共同発明者の氏名	Full name of sixth joint inventor, If any Susumu SATOH
第六の共同発明者の署名　日付	Sixth inventor's signature　Date
住所	Residence 6-19-11, Kinunodai, Yawara-mura, Tsukuba-gun, Ibaraki 300-2436, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第三の共同発明者の氏名	Full name of seventh joint inventor, If any Hiroyuki ARAKAWA
第三の共同発明者の署名　日付	Seventh inventor's signature　Date
住所	Residence 1-22-9, Kannondai, Tsukuba-shi, Ibaraki 305-0856, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of eighth joint inventor, If any Masahiko MORITA
第四の共同発明者の署名　日付	Eighth inventor's signature　Date
住所	Residence 1-20-1-2-103, Chuo, Ushiku-shi, Ibaraki 300-1234, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

DOCKET NO. 217925US0XPCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: Toshio OTA, et al

SERIAL NO. : 10/030,269

FILING DATE : January 8, 2002

FOR: **AMYLOID-β PROTEIN AGGREGATION-REGULATING FACTORS**

DECLARATION OF Yuri HIO

I, Yuri HIO am the fourth-named inventor of the above-identified application which is the national phase of PCT U.S. Application based on PCT/JP00/04515 filed July 6, 2000.

Subsequent to the filing of the International application, I have married and changed my surname. Specifically, my maiden name in the International application is "**KAWAI**". My true and correct married name, **Yuri HIO**, has been set forth on the Declaration, Power of Attorney and Petition filed herewith.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: May 30, 2002

Yuri Hio

Yuri HIO
(Married Name)

Yuri Kawai

Formerly Yuri KAWAI
(Maiden Name)

4508-19-201, Yana, Kisarazu-shi, Chiba, 292-0812, JAPAN

217925US0XPCT

Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

As a below named inventor, I hereby declare that:

私の住所、郵便の宛先、国籍は下記の私の氏名の後に記載された通りです。

My residence, mailing address and citizenship are as stated next to my name.

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

AMYLOID-β PROTEIN AGGREGATION-REGULATING FACTORS (as amended)

上記発明の明細書は、

the specification of which

☐ 本書に添付されています。

☐ is attached hereto.

☐ _____ 月 _____ 日に提出され、米国出願番号または特許協定条約国際出願番号を

_____ とし、

（該当する場合） _____ に訂正されました。

☒ was filed on July 6, 2000

as United States Application Number or PCT International Application Number

PCT/JP00/04515 and was amended on

_____ (if applicable)

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は、連邦規則法典第37編第1条56項に定義されるとおり、特許資格の有無について重要な情報を開示する義務があることを認めます。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Japanese Language Declaration
(日本語宣言書)

私は、米国法典第 35 編 119 条(a) – (d)項又は 365 条 (b) 項
に基づき下記の、米国以外の国の少なくとも一ヵ国を指定している特許協力条約 365(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

I hereby claim foreign priority under Title 35, United States Code, § 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)
外国での先行出願

(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	Priority Claimed 優先権主張 Yes はい	No いいえ
11/194179	Japan	8 July 1999	☒	☐

私は、第 35 編米国法典 119 条 (e) 項に基づいて下記の米国特許出願規定に記載された権利をここに主張いたします。

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)
60/159,586	18 October 1999

私は、下記の米国法典第 35 編 120 条に基づいて下記の米国特許出願に記載された権利、又は米国を指定している特許協力条約 365 条 (c) に基づく権利をここに主張します。また、
本出願の各請求範囲の内容が米国法典第 35 編 112 条第 1 項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内または特許協力条約国際提出日までの期間中に入手された、連邦規則法典第 37 編 1 条 56 項で定義さ
れた特許資格の有無に関する重要な情報について開示義務があることを認識しています。

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(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)
PCT/JP00/04515	6 July 2000	Pending

私は、私自身の知識に基づいて本宣言書中で私が行なう表明が真実であり、かつ私の入手した情報と私の信じるところに基づく表明が全て真実であると信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第 18 編第 1001 条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行なえば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration
(日本語宣言書)

委任状：私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。
（弁護士、または代理人の指名及び登録番号を明記のこと）

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)

022850

書類送付先

Send Correspondence to:

022850

直接電話連絡先：（名前及び電話番号）

Direct Telephone calls to: (name and telephone number)

(703) 413-3000

単独発明者または第一の共同発明者の氏名	Full name of sole or first inventor Toshio OTA
発明者の署名　日付	Inventor's signature　Date
住所	Residence c/o Kyowa Hakko Kogyo Co., Ltd., Tokyo Research Laboratories, 3-6-6, Asahi-machi, Machida-shi, Tokyo 194-8533, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

第二の共同発明者の氏名	Full name of second joint inventor, If any Takao ISOGAI
第二の共同発明者の署名　日付	Second inventor's signature　Date
住所	Residence 511-12, Omuro, Ami-machi, Inashiki-gun, Ibaraki 300-0303, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

SEQUENCE LISTING

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Ser Val Val Gly Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val
100 105 110

Asp Pro Leu Ile Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn
115 120 125

Glu Glu Glu Asn Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ala Ser
130 135 140

Leu Gly Gly Pro Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala
145 150 155 160

Gln Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Thr Val Phe
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Asp Arg His Lys Met Leu Ser
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Met Ala Ala Ala Ala Val Ser Gly Ala Leu
1 5 10

ggc cgg gcg ggc tgg agg ctc ctg cag ctg cga tgc ctg ccc gtg gcc 160
Gly Arg Ala Gly Trp Arg Leu Leu Gln Leu Arg Cys Leu Pro Val Ala
15 20 25

cgt tgc cga caa gcc ctg gtg ccg cgt gcc ttc cat gct tca gct gtg 208
Arg Cys Arg Gln Ala Leu Val Pro Arg Ala Phe His Ala Ser Ala Val
30 35 40

ggg cta agg tct tca gat gag cag aag cag cag cct ccc aac tca ttt 256
Gly Leu Arg Ser Ser Asp Glu Gln Lys Gln Gln Pro Pro Asn Ser Phe
45 50 55

tct cag cag cat tct gag aca cag ggc gca gaa aaa cct gat cca gag 304

Ser Gln Gln His Ser Glu Thr Gln Gly Ala Glu Lys Pro Asp Pro Glu
60 65 70

tct tct cat tca ccc ccc agg tat aca gac cag ggc ggc gag gag gag 352
Ser Ser His Ser Pro Pro Arg Tyr Thr Asp Gln Gly Gly Glu Glu Glu
75 80 85 90

gag gac tat gaa agt gag gag cag ttg cag cac cgc atc ctg acg gca 400
Glu Asp Tyr Glu Ser Glu Glu Gln Leu Gln His Arg Ile Leu Thr Ala
95 100 105

gcc ctt gag ttt gtg ccc gcc cac ggg tgg aca gca gag gcg att gca 448
Ala Leu Glu Phe Val Pro Ala His Gly Trp Thr Ala Glu Ala Ile Ala
110 115 120

gaa gga gcc cag gtg tgt ata ggt gag ggt ggg gcc acc taaccaagat 497
Glu Gly Ala Gln Val Cys Ile Gly Glu Gly Gly Ala Thr
125 130 135

gagccaggat ggagtcacac caggcagagc gggggcctc atgccttctt ccagtctagc 557

tcagagcccc tcacagctgc aagattgact ggtttttttc ccccaatagg gtggaactgg 617

ctttattttg tagttataaa gaacatacca tggagttggt tcttgggagt tgtgttctaa 677

aggcaatcta ttaggcaaga attgtctgtg atcaaaactc ccatgtttca ttgactctaa 737

gatgccattg gttgtaagaa gcatcatttt taaatgcatc agtaaaaaag aaaacatact 797

gcccttcgaa ctatgacaaa gcacttctgt gattcacact gatttttttaa aatgaaaaat 857

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gactgctgct ttagattagg cagcaggctc atgttcaggc catgttgtag agaatcctcc 1037

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aaatatatac aaatgtttac ttagaagatg tggtaagtgc tatcaaggaa aggtgctgtt 1577

gggctgtata atggagggac ccgatcatta gatcaggtca cagctgcgag attgactggt 1637

ttctttccct caatagggtg gaaatggctt tattttgtgg atataaaagt aatgaaccat 1697

ggaattggtt cttgagagtt gtgttctaaa ggcaacctat tggcaagaat tgtctgtgat 1757

caaaactacc atatttcatt gactctaaga tgccattggt tgtaagaagc actattttta 1817

agtacatcag t 1828

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<213> Homo sapiens

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20 25 30

Val Pro Arg Ala Phe His Ala Ser Ala Val Gly Leu Arg Ser Ser Asp
35 40 45

Glu Gln Lys Gln Gln Pro Pro Asn Ser Phe Ser Gln Gln His Ser Glu
50 55 60

Thr Gln Gly Ala Glu Lys Pro Asp Pro Glu Ser Ser His Ser Pro Pro
65 70 75 80

Arg Tyr Thr Asp Gln Gly Gly Glu Glu Glu Glu Asp Tyr Glu Ser Glu
85 90 95

Glu Gln Leu Gln His Arg Ile Leu Thr Ala Ala Leu Glu Phe Val Pro
100 105 110

Ala His Gly Trp Thr Ala Glu Ala Ile Ala Glu Gly Ala Gln Val Cys
115 120 125

Ile Gly Glu Gly Gly Ala Thr
130 135

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Met Leu Pro Pro Leu
1 5

ccc tcc cgc ctc ggg ctg ctg ctg ctg ctg ctc ctg tgc ccg gcg cac 162
Pro Ser Arg Leu Gly Leu Leu Leu Leu Leu Leu Cys Pro Ala His
10 15 20

gtc ggc gga ctg tgg tgg gct gtg ggc agc ccc ttg gtt atg gac cct 210
Val Gly Gly Leu Trp Trp Ala Val Gly Ser Pro Leu Val Met Asp Pro
25 30 35

acc agc atc tgc agg aag gca cgg cgg ctg gcc ggg cgg cag gcc gag 258
Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala Gly Arg Gln Ala Glu
40 45 50

ttg tgc cag gct gag ccg gaa gtg gtg gca gag cta gct cgg ggc gcc 306
Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu Leu Ala Arg Gly Ala
55 60 65

cgg ctc ggg gtg cga gag tgc cag ttc cag ttc cgc ttc cgc cgc tgg 354

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Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe Arg Phe Arg Arg Trp
70                  75                  80                  85

aat tgc tcc agc cac agc aag gcc ttt gga cgc atc ctg caa cag gac      402
Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg Ile Leu Gln Gln Asp
                90                  95                  100

att cgg gag acg gcc ttc gtg ttc gcc atc act gcg gcc ggc gcc agc      450
Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr Ala Ala Gly Ala Ser
            105                 110                 115

cac gcc gtc acg cag gcc tgt tct atg ggc gag ctg ctg cag tgc ggc      498
His Ala Val Thr Gln Ala Cys Ser Met Gly Glu Leu Leu Gln Cys Gly
        120                 125                 130

tgc cag gcg ccc cgc tgg cgg gcc cct ccc cgg ccc tcc ggc ctg ccc      546
Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg Pro Ser Gly Leu Pro
    135                 140                 145

ggc acc ccc gga ccc cct ggc ccc gcg ggc tcc ccg gaa ggc agc gcc      594
Gly Thr Pro Gly Pro Pro Gly Pro Ala Gly Ser Pro Glu Gly Ser Ala
150                 155                 160                 165

gcc tgg gag tgg gga ggc tgc ggc gac gac gtg gac ttc ggg gac gag      642
Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val Asp Phe Gly Asp Glu
                170                 175                 180

aag tcg agg ctc ttt atg gac gcg cgg cac aag cgg gga cgc gga gac      690
Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys Arg Gly Arg Gly Asp
            185                 190                 195

atc cgc gcg ttg gtg caa ctg cac aac aac gag gcg ggc agg ctg gcc      738
Ile Arg Ala Leu Val Gln Leu His Asn Asn Glu Ala Gly Arg Leu Ala
        200                 205                 210

gtg cgg agc cac acg cgc acc gag tgc aaa tgc cac ggg ctg tcg gga      786
Val Arg Ser His Thr Arg Thr Glu Cys Lys Cys His Gly Leu Ser Gly
    215                 220                 225

tca tgc gcg ctg cgc acc tgc tgg cag aag ctg cct cca ttt cgc gag      834
Ser Cys Ala Leu Arg Thr Cys Trp Gln Lys Leu Pro Pro Phe Arg Glu
230                 235                 240                 245

gtg ggc gcg cgg ctg ctg gag cgc ttc cac ggc gcc tca cgc gtc atg      882
Val Gly Ala Arg Leu Leu Glu Arg Phe His Gly Ala Ser Arg Val Met
                250                 255                 260

ggc acc aac gac ggc aag gcc ctg ctg ccc gcc gtc cgc acg ctc aag      930
Gly Thr Asn Asp Gly Lys Ala Leu Leu Pro Ala Val Arg Thr Leu Lys
            265                 270                 275

ccg ccg ggc cga gcg gac ctc ctc tac gcc gcc gat tcg ccc gac ttc      978
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Pro Pro Gly Arg Ala Asp Leu Leu Tyr Ala Ala Asp Ser Pro Asp Phe
        280                 285                 290

tgc gcc ccc aac cga cgc acc ggc tcc ccc ggc acg cgc ggt cgc gcc     1026
Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly Thr Arg Gly Arg Ala
    295                 300                 305

tgc aat agc agc gcc ccg gac ctc agc ggc tgc gac ctg ctg tgc tgc     1074
Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys Asp Leu Leu Cys Cys
310                 315                 320                 325

ggc cgc ggg cac cgc cag gag agc gtg cag ctc gaa gag aac tgc ctg     1122
Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu Glu Glu Asn Cys Leu
                330                 335                 340

tgc cgc ttc cac tgg tgc tgc gta gta cag tgc cac cgc tgc cgt gtg     1170
Cys Arg Phe His Trp Cys Cys Val Val Gln Cys His Arg Cys Arg Val
            345                 350                 355

cgc aag gag ctc agc ctc tgc ctg tgacccgccg cccggccgct agactgactt    1224
Arg Lys Glu Leu Ser Leu Cys Leu
        360                 365

cgcgcagcgg tggctcgcac ctgtgggacc tcagggcacc ggcaccgggc gcctctcgcc   1284

gctcgagccc agcctctccc tgccaaagcc caactcccag ggctctggaa atggtgaggc   1344

gaggggcttg agaggaacgc ccacccacga aggcccaggg cgccagacgg ccccgaaaag   1404

gcgctcgggg agcgtttaaa ggacactgta caggccctcc ctccccttgg cctctaggag   1464

gaaacagttt tttagactgg aaaaaagcca gtctaaaggc ctctggatac tgggctcccc   1524

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Leu Cys Pro Ala His Val Gly Gly Leu Trp Trp Ala Val Gly Ser Pro
            20                  25                  30

Leu Val Met Asp Pro Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala
        35                  40                  45

Gly Arg Gln Ala Glu Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu
    50                  55                  60

Leu Ala Arg Gly Ala Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe
65                  70                  75                  80

Arg Phe Arg Arg Trp Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg
                85                  90                  95

Ile Leu Gln Gln Asp Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr
            100                 105                 110

Ala Ala Gly Ala Ser His Ala Val Thr Gln Ala Cys Ser Met Gly Glu
        115                 120                 125

Leu Leu Gln Cys Gly Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg
    130                 135                 140

Pro Ser Gly Leu Pro Gly Thr Pro Gly Pro Pro Gly Pro Ala Gly Ser
145                 150                 155                 160

Pro Glu Gly Ser Ala Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val
                165                 170                 175

Asp Phe Gly Asp Glu Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys
            180                 185                 190

Arg Gly Arg Gly Asp Ile Arg Ala Leu Val Gln Leu His Asn Asn Glu
        195                 200                 205

Ala Gly Arg Leu Ala Val Arg Ser His Thr Arg Thr Glu Cys Lys Cys
    210                 215                 220
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His Gly Leu Ser Gly Ser Cys Ala Leu Arg Thr Cys Trp Gln Lys Leu
225 230 235 240

Pro Pro Phe Arg Glu Val Gly Ala Arg Leu Leu Glu Arg Phe His Gly
245 250 255

Ala Ser Arg Val Met Gly Thr Asn Asp Gly Lys Ala Leu Leu Pro Ala
260 265 270

Val Arg Thr Leu Lys Pro Pro Gly Arg Ala Asp Leu Leu Tyr Ala Ala
275 280 285

Asp Ser Pro Asp Phe Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly
290 295 300

Thr Arg Gly Arg Ala Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys
305 310 315 320

Asp Leu Leu Cys Cys Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu
325 330 335

Glu Glu Asn Cys Leu Cys Arg Phe His Trp Cys Cys Val Val Gln Cys
340 345 350

His Arg Cys Arg Val Arg Lys Glu Leu Ser Leu Cys Leu
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ttctcagcgc tgattttgag atg atg ggc ttg gga aac ggg cgt cgc agc atg     173
                      Met Met Gly Leu Gly Asn Gly Arg Arg Ser Met
                      1               5                   10

aag tcg ccg ccc ctc gtg ctg gcc gcc ctg gtg gcc tgc atc atc gtc       221
Lys Ser Pro Pro Leu Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val
            15                  20                  25

ttg ggc ttc aac tac tgg att gcg agc tcc cgg agc gtg gac ctc cag       269
Leu Gly Phe Asn Tyr Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln
        30                  35                  40

aca cgg atc atg gag ctg gaa ggc agg gtc cgc agg gcg gct gca gag       317
Thr Arg Ile Met Glu Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu
    45                  50                  55

aga ggc gcc gtg gag ctg aag aag aac gag ttc cag gga gag ctg gag       365
Arg Gly Ala Val Glu Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu
60                  65                  70                  75

aag cag cgg gag cag ctt gac aaa atc cag tcc agc cac aac ttc cag       413
Lys Gln Arg Glu Gln Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln
                80                  85                  90

ctg gag agc gtc aac aag ctg tac cag gac gaa aag gcg gtt ttg gtg       461
Leu Glu Ser Val Asn Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val
            95                  100                 105

aat aac atc acc aca ggt gag agg ctc atc cga gtg ctg caa gac cag       509
Asn Asn Ile Thr Thr Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln
        110                 115                 120

tta aag acc ctg cag agg aat tac ggc agg ctg cag cag gat gtc ctc       557
Leu Lys Thr Leu Gln Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu
    125                 130                 135

cag ttt cag aag aac cag acc aac ctg gag agg aag ttc tcc tac gac       605
Gln Phe Gln Lys Asn Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp
140                 145                 150                 155

ctg agc cag tgc atc aat cag atg aag gag gtg aag gaa cag tgt gag       653
Leu Ser Gln Cys Ile Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu
                160                 165                 170
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gag cga ata gaa gag gtc acc aaa aag ggg aat gaa gct gta gct tcc      701
Glu Arg Ile Glu Glu Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser
            175                 180                 185

aga gac ctg agt gaa aac aac gac cag aga cag cag ctc caa gcc ctc      749
Arg Asp Leu Ser Glu Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu
        190                 195                 200

agt gag cct cag ccc agg ctg cag gca gca ggc ctg cca cac aca gag      797
Ser Glu Pro Gln Pro Arg Leu Gln Ala Ala Gly Leu Pro His Thr Glu
    205                 210                 215

gtg cca caa ggg aag gga aac gtg ctt ggt aac agc aag tcc cag aca      845
Val Pro Gln Gly Lys Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr
220                 225                 230                 235

cca gcc ccc agt tcc gaa gtg gtt ttg gat tca aag aga caa gtt gag      893
Pro Ala Pro Ser Ser Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu
                240                 245                 250

aaa gag gaa acc aat gag atc cag gtg gtg aat gag gag cct cag agg      941
Lys Glu Glu Thr Asn Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg
            255                 260                 265

gac agg ctg ccg cag gag cca ggc cgg gag cag gtg gtg gaa gac aga      989
Asp Arg Leu Pro Gln Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg
        270                 275                 280

cct gta ggt gga aga ggc ttc ggg gga gcc gga gaa ctg ggc cag acc     1037
Pro Val Gly Gly Arg Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr
    285                 290                 295

cca cag gtg cag gct gcc ctg tca gtg agc cag gaa aat cca gag atg     1085
Pro Gln Val Gln Ala Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met
300                 305                 310                 315

gag ggc cct gag cga gac cag ctt gtc atc ccc gac gga cag gag gag     1133
Glu Gly Pro Glu Arg Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu
                320                 325                 330

gag cag gaa gct gcc ggg gaa ggg aga aac cag cag aaa ctg aga gga     1181
Glu Gln Glu Ala Ala Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly
            335                 340                 345

gaa gat gac tac aac atg gat gaa aat gaa gca gaa tct gag aca gac     1229
Glu Asp Asp Tyr Asn Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp
        350                 355                 360

aag caa gca gcc ctg gca ggg aat gac aga aac ata gat gtt ttt aat     1277
Lys Gln Ala Ala Leu Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn
    365                 370                 375
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gtt gaa gat cag aaa aga gac acc ata aat tta ctt gat cag cgt gaa      1325
Val Glu Asp Gln Lys Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu
380                 385                 390                 395

aag cgg aat cat aca ctc tgaattgaac tggaatcaca tatttcacaa             1373
Lys Arg Asn His Thr Leu
                400

cagggccgaa gagatgactt taaaatgttc atgagggact gaatactgaa aactgtgaaa   1433

tgtactaaat aaaatgtaca tctgaagatg attattgtga aattttagta tgcactttgt   1493

gtaggaaaaa atggaatggt cttttaaaca gcttttgggg ggtactttgg aagtgtctaa   1553

taaggtgtca caatttttgg tagtaggtat ttcgtgagaa gctcaacacc aaaactggaa   1613

catagttctc cttcaagtgt tggcgacagc ggggcttcct gattctggaa tataactttg   1673

tgtaaattaa cagccaccta tagaagagtc catctgctgt gaaggagaga cagagaactc   1733

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atcaatggcc tagagcactg actgttaaca caaacgtcac tagcaaagta gcaacagctt   1913

taagtctaaa tacaaagctg ttctgtgtga gaatttttta aaaggctact tgtataataa   1973

cccttgtcat ttttaatgta caaaacgcta ttaagtggct tagaatttga acatttgtgg   2033

tctttattta ctttgcttcg tgtgtgggca aagcaacatc ttccctaaat atatattacc   2093

aagaaaagca agaagcagat taggtttttg acaaaacaaa caggccaaaa gggggctgac   2153

ctggagcaga gcatggtgag aggcaaggca tgagagggca agttttgttg tggacagatc   2213

tgtgcctact ttattactgg agtaaaagaa aacaaagttc attgatgtcg aaggatatat   2273

acagtgttag aaattaggac tgtttagaaa aacaggaata caatggttgt ttttatcata   2333

gtgtacacat ttagcttgtg gtaaatgact cacaaaactg attttaaaat caagttaatg   2393

tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac   2453

ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg   2513

ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca   2573

caggatttga gatgctaagg ccccagagat cgtttgaacc aaccctctta ttttcagagg   2633

ggaaaatggg gcctagaagt tacagagcat ctagctggtg cgctggcacc cctggcctca   2693
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cacagactcc cgagtagctg ggactacagg cacacagtca ctgaagcagg ccctgtttgc 2753

aattcacgct gccacctcca acttaaacat tcttcatatg tgatgtcctt agtcactaag 2813

gttaaacttt cccacccaga aaaggcaact tagataaaat cttagagtac tttcatactc 2873

ttctaagtcc tcttccagcc tcactttgag tcctccttgg ggttgatagg aattttctct 2933

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<213> Homo sapiens

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Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val Leu Gly Phe Asn Tyr
20 25 30

Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln Thr Arg Ile Met Glu
35 40 45

Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu Arg Gly Ala Val Glu
50 55 60

Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu Lys Gln Arg Glu Gln
65 70 75 80

Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln Leu Glu Ser Val Asn
85 90 95

Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val Asn Asn Ile Thr Thr
100 105 110

Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln Leu Lys Thr Leu Gln
115 120 125

Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu Gln Phe Gln Lys Asn
130 135 140

Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp Leu Ser Gln Cys Ile
145 150 155 160

Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu Glu Arg Ile Glu Glu
165 170 175

Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser Arg Asp Leu Ser Glu
180 185 190

Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu Ser Glu Pro Gln Pro
195 200 205

Arg Leu Gln Ala Ala Gly Leu Pro His Thr Glu Val Pro Gln Gly Lys
210 215 220

Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr Pro Ala Pro Ser Ser
225 230 235 240

Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu Lys Glu Glu Thr Asn
245 250 255

Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg Asp Arg Leu Pro Gln
260 265 270

Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg Pro Val Gly Gly Arg
275 280 285

Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr Pro Gln Val Gln Ala
290 295 300

Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met Glu Gly Pro Glu Arg
305 310 315 320

Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu Glu Gln Glu Ala Ala
325 330 335

Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly Glu Asp Asp Tyr Asn
340 345 350

Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp Lys Gln Ala Ala Leu
355 360 365

Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn Val Glu Asp Gln Lys
370 375 380

Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu Lys Arg Asn His Thr
385 390 395 400

Leu

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<212> DNA

<213> Homo sapiens

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<222> (40)..(1875)

<223>

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atg gtc ctg gtg gaa att ctg gac gtg aat gac aat gtc cct gaa gta 102
Met Val Leu Val Glu Ile Leu Asp Val Asn Asp Asn Val Pro Glu Val
10 15 20

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atg gtt act tca ctg tcg ctc cct gtg caa gag gat gct cag gtg ggt      150
Met Val Thr Ser Leu Ser Leu Pro Val Gln Glu Asp Ala Gln Val Gly
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Thr Val Ile Ala Leu Ile Ser Val Ser Asp Arg Asp Ser Gly Ala Asn
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His Val Gly Leu Tyr Thr Gly Glu Ile Ser Thr Thr Arg Ile Leu Asp
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SATOH, SUSUMU
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ccaggcttgc tgcagggcat ctacccatgg acaatgggca aggttgctgc tttactgaaa
1157

tttaactgtt atttccttgt cttctctcac tcccaagtgc acatttggta acagaagtct
1217

cattagtgaa atgtgggtgc tctgactcca ctgtaggctc attgtgaaaa ctgaacaata
1277

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1337

aacatttatg cctagatctt tccaattaaa acccttttata tgattcattc tttaaatgtt
1397

tattgagcaa ataatgtgcc ctaggcactg tgctagtcca agagacatga caggggtcaa
1457

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1517

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1577

gggctgtata atggagggac ccgatcatta gatcaggtca cagctgcgag attgactggt

1637

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1697

ggaattggtt cttgagagtt gtgttctaaa ggcaacctat tggcaagaat tgtctgtgat
1757

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1817

agtacatcag t
1828

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<213> Homo sapiens

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20 25 30

Val Pro Arg Ala Phe His Ala Ser Ala Val Gly Leu Arg Ser Ser Asp
35 40 45

Glu Gln Lys Gln Gln Pro Pro Asn Ser Phe Ser Gln Gln His Ser Glu
50 55 60

Thr Gln Gly Ala Glu Lys Pro Asp Pro Glu Ser Ser His Ser Pro Pro
65 70 75 80

Arg Tyr Thr Asp Gln Gly Gly Glu Glu Glu Glu Asp Tyr Glu Ser Glu
85 90 95

Glu Gln Leu Gln His Arg Ile Leu Thr Ala Ala Leu Glu Phe Val Pro
100 105 110

Ala His Gly Trp Thr Ala Glu Ala Ile Ala Glu Gly Ala Gln Val Cys
115 120 125

Ile Gly Glu Gly Gly Ala Thr
130 135

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114
Met Leu Pro Pro Leu
1 5

ccc tcc cgc ctc ggg ctg ctg ctg ctg ctg ctc ctg tgc ccg gcg cac
162
Pro Ser Arg Leu Gly Leu Leu Leu Leu Leu Leu Cys Pro Ala His
10 15 20

gtc ggc gga ctg tgg tgg gct gtg ggc agc ccc ttg gtt atg gac cct
210
Val Gly Gly Leu Trp Trp Ala Val Gly Ser Pro Leu Val Met Asp Pro
25 30 35

acc agc atc tgc agg aag gca cgg cgg ctg gcc ggg cgg cag gcc gag
258
Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala Gly Arg Gln Ala Glu
40 45 50

ttg tgc cag gct gag ccg gaa gtg gtg gca gag cta gct cgg ggc gcc
306
Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu Leu Ala Arg Gly Ala

55 60 65

cgg ctc ggg gtg cga gag tgc cag ttc cag ttc cgc ttc cgc cgc tgg
354
Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe Arg Phe Arg Arg Trp
70 75 80 85

aat tgc tcc agc cac agc aag gcc ttt gga cgc atc ctg caa cag gac
402
Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg Ile Leu Gln Gln Asp
90 95 100

att cgg gag acg gcc ttc gtg ttc gcc atc act gcg gcc ggc gcc agc
450
Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr Ala Ala Gly Ala Ser
105 110 115

cac gcc gtc acg cag gcc tgt tct atg ggc gag ctg ctg cag tgc ggc
498
His Ala Val Thr Gln Ala Cys Ser Met Gly Glu Leu Leu Gln Cys Gly
120 125 130

tgc cag gcg ccc cgc tgg cgg gcc cct ccc cgg ccc tcc ggc ctg ccc
546
Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg Pro Ser Gly Leu Pro
135 140 145

ggc acc ccc gga ccc cct ggc ccc gcg ggc tcc ccg gaa ggc agc gcc
594
Gly Thr Pro Gly Pro Pro Gly Pro Ala Gly Ser Pro Glu Gly Ser Ala
150 155 160 165

gcc tgg gag tgg gga ggc tgc ggc gac gac gtg gac ttc ggg gac gag
642
Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val Asp Phe Gly Asp Glu
170 175 180

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aag tcg agg ctc ttt atg gac gcg cgg cac aag cgg gga cgc gga gac
    690
Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys Arg Gly Arg Gly Asp

            185                 190                 195

atc cgc gcg ttg gtg caa ctg cac aac aac gag gcg ggc agg ctg gcc
    738
Ile Arg Ala Leu Val Gln Leu His Asn Asn Glu Ala Gly Arg Leu Ala

        200                 205                 210

gtg cgg agc cac acg cgc acc gag tgc aaa tgc cac ggg ctg tcg gga
    786
Val Arg Ser His Thr Arg Thr Glu Cys Lys Cys His Gly Leu Ser Gly

    215                 220                 225

tca tgc gcg ctg cgc acc tgc tgg cag aag ctg cct cca ttt cgc gag
    834
Ser Cys Ala Leu Arg Thr Cys Trp Gln Lys Leu Pro Pro Phe Arg Glu

230                 235                 240                 245

gtg ggc gcg cgg ctg ctg gag cgc ttc cac ggc gcc tca cgc gtc atg
    882
Val Gly Ala Arg Leu Leu Glu Arg Phe His Gly Ala Ser Arg Val Met

                250                 255                 260

ggc acc aac gac ggc aag gcc ctg ctg ccc gcc gtc cgc acg ctc aag
    930
Gly Thr Asn Asp Gly Lys Ala Leu Leu Pro Ala Val Arg Thr Leu Lys

            265                 270                 275

ccg ccg ggc cga gcg gac ctc ctc tac gcc gcc gat tcg ccc gac ttc
    978
Pro Pro Gly Arg Ala Asp Leu Leu Tyr Ala Ala Asp Ser Pro Asp Phe

        280                 285                 290

tgc gcc ccc aac cga cgc acc ggc tcc ccc ggc acg cgc ggt cgc gcc
   1026
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Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly Thr Arg Gly Arg Ala
295 300 305

tgc aat agc agc gcc ccg gac ctc agc ggc tgc gac ctg ctg tgc tgc
1074
Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys Asp Leu Leu Cys Cys
310 315 320 325

ggc cgc ggg cac cgc cag gag agc gtg cag ctc gaa gag aac tgc ctg
1122
Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu Glu Glu Asn Cys Leu
330 335 340

tgc cgc ttc cac tgg tgc tgc gta gta cag tgc cac cgc tgc cgt gtg
1170
Cys Arg Phe His Trp Cys Cys Val Val Gln Cys His Arg Cys Arg Val
345 350 355

cgc aag gag ctc agc ctc tgc ctg tgacccgccg cccggccgct agactgactt
1224
Arg Lys Glu Leu Ser Leu Cys Leu
360 365

cgcgcagcgg tggctcgcac ctgtgggacc tcagggcacc ggcaccgggc gcctctcgcc
1284

gctcgagccc agcctctccc tgccaaagcc caactcccag ggctctggaa atggtgaggc
1344

gaggggcttg agaggaacgc ccacccacga aggcccaggg cgccagacgg ccccgaaaag
1404

gcgctcgggg agcgtttaaa ggacactgta caggccctcc ctccccttgg cctctaggag
1464

gaaacagttt tttagactgg aaaaaagcca gtctaaaggc ctctggatac tgggctcccc
1524

agaactgctg gccacaggat ggtgggtgag gttagtatca ataaagatat ttaaaccacc
1584

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<211> 365
<212> PRT
<213> Homo sapiens

<400> 6

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20 25 30

Leu Val Met Asp Pro Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala
35 40 45

Gly Arg Gln Ala Glu Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu
50 55 60

Leu Ala Arg Gly Ala Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe
65 70 75 80

Arg Phe Arg Arg Trp Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg
85 90 95

Ile Leu Gln Gln Asp Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr
100 105 110

Ala Ala Gly Ala Ser His Ala Val Thr Gln Ala Cys Ser Met Gly Glu
115 120 125

Leu Leu Gln Cys Gly Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg
130 135 140

Pro Ser Gly Leu Pro Gly Thr Pro Gly Pro Pro Gly Pro Ala Gly Ser
145 150 155 160

Pro Glu Gly Ser Ala Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val
165 170 175

Asp Phe Gly Asp Glu Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys

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                180                 185                 190

Arg Gly Arg Gly Asp Ile Arg Ala Leu Val Gln Leu His Asn Asn Glu
        195                 200                 205

Ala Gly Arg Leu Ala Val Arg Ser His Thr Arg Thr Glu Cys Lys Cys
    210                 215                 220

His Gly Leu Ser Gly Ser Cys Ala Leu Arg Thr Cys Trp Gln Lys Leu
225                 230                 235                 240

Pro Pro Phe Arg Glu Val Gly Ala Arg Leu Leu Glu Arg Phe His Gly
                245                 250                 255

Ala Ser Arg Val Met Gly Thr Asn Asp Gly Lys Ala Leu Leu Pro Ala
            260                 265                 270

Val Arg Thr Leu Lys Pro Pro Gly Arg Ala Asp Leu Leu Tyr Ala Ala
        275                 280                 285

Asp Ser Pro Asp Phe Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly
    290                 295                 300

Thr Arg Gly Arg Ala Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys
305                 310                 315                 320

Asp Leu Leu Cys Cys Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu
                325                 330                 335

Glu Glu Asn Cys Leu Cys Arg Phe His Trp Cys Cys Val Val Gln Cys
            340                 345                 350

His Arg Cys Arg Val Arg Lys Glu Leu Ser Leu Cys Leu
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120

ttctcagcgc tgattttgag atg atg ggc ttg gga aac ggg cgt cgc agc atg
173
Met Met Gly Leu Gly Asn Gly Arg Arg Ser Met
1 5 10

aag tcg ccg ccc ctc gtg ctg gcc gcc ctg gtg gcc tgc atc atc gtc
221
Lys Ser Pro Pro Leu Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val
15 20 25

ttg ggc ttc aac tac tgg att gcg agc tcc cgg agc gtg gac ctc cag
269
Leu Gly Phe Asn Tyr Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln
30 35 40

aca cgg atc atg gag ctg gaa ggc agg gtc cgc agg gcg gct gca gag
317
Thr Arg Ile Met Glu Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu
45 50 55

aga ggc gcc gtg gag ctg aag aag aac gag ttc cag gga gag ctg gag
365
Arg Gly Ala Val Glu Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu
60 65 70 75

aag cag cgg gag cag ctt gac aaa atc cag tcc agc cac aac ttc cag
413
Lys Gln Arg Glu Gln Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln

80 85 90

ctg gag agc gtc aac aag ctg tac cag gac gaa aag gcg gtt ttg gtg
461
Leu Glu Ser Val Asn Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val
95 100 105

aat aac atc acc aca ggt gag agg ctc atc cga gtg ctg caa gac cag
509
Asn Asn Ile Thr Thr Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln
110 115 120

tta aag acc ctg cag agg aat tac ggc agg ctg cag cag gat gtc ctc
557
Leu Lys Thr Leu Gln Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu
125 130 135

cag ttt cag aag aac cag acc aac ctg gag agg aag ttc tcc tac gac
605
Gln Phe Gln Lys Asn Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp
140 145 150 155

ctg agc cag tgc atc aat cag atg aag gag gtg aag gaa cag tgt gag
653
Leu Ser Gln Cys Ile Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu
160 165 170

gag cga ata gaa gag gtc acc aaa aag ggg aat gaa gct gta gct tcc
701
Glu Arg Ile Glu Glu Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser
175 180 185

aga gac ctg agt gaa aac aac gac cag aga cag cag ctc caa gcc ctc
749
Arg Asp Leu Ser Glu Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu
190 195 200

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agt gag cct cag ccc agg ctg cag gca gca ggc ctg cca cac aca gag
    797
Ser Glu Pro Gln Pro Arg Leu Gln Ala Ala Gly Leu Pro His Thr Glu

    205                 210                 215

gtg cca caa ggg aag gga aac gtg ctt ggt aac agc aag tcc cag aca
    845
Val Pro Gln Gly Lys Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr

220                 225                 230                 235

cca gcc ccc agt tcc gaa gtg gtt ttg gat tca aag aga caa gtt gag
    893
Pro Ala Pro Ser Ser Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu

                240                 245                 250

aaa gag gaa acc aat gag atc cag gtg gtg aat gag gag cct cag agg
    941
Lys Glu Glu Thr Asn Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg

            255                 260                 265

gac agg ctg ccg cag gag cca ggc cgg gag cag gtg gtg gaa gac aga
    989
Asp Arg Leu Pro Gln Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg

        270                 275                 280

cct gta ggt gga aga ggc ttc ggg gga gcc gga gaa ctg ggc cag acc
   1037
Pro Val Gly Gly Arg Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr

    285                 290                 295

cca cag gtg cag gct gcc ctg tca gtg agc cag gaa aat cca gag atg
   1085
Pro Gln Val Gln Ala Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met

300                 305                 310                 315

gag ggc cct gag cga gac cag ctt gtc atc ccc gac gga cag gag gag
   1133
Glu Gly Pro Glu Arg Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu
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320 325 330

gag cag gaa gct gcc ggg gaa ggg aga aac cag cag aaa ctg aga gga
1181
Glu Gln Glu Ala Ala Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly

335 340 345

gaa gat gac tac aac atg gat gaa aat gaa gca gaa tct gag aca gac
1229
Glu Asp Asp Tyr Asn Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp

350 355 360

aag caa gca gcc ctg gca ggg aat gac aga aac ata gat gtt ttt aat
1277
Lys Gln Ala Ala Leu Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn

365 370 375

gtt gaa gat cag aaa aga gac acc ata aat tta ctt gat cag cgt gaa
1325
Val Glu Asp Gln Lys Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu

380 385 390 395

aag cgg aat cat aca ctc tgaattgaac tggaatcaca tatttcacaa
1373
Lys Arg Asn His Thr Leu

400

cagggccgaa gagatgactt taaaatgttc atgagggact gaatactgaa aactgtgaaa
1433

tgtactaaat aaaatgtaca tctgaagatg attattgtga aattttagta tgcactttgt
1493

gtaggaaaaa atggaatggt cttttaaaca gcttttgggg ggtactttgg aagtgtctaa
1553

taaggtgtca caatttttgg tagtaggtat ttcgtgagaa gctcaacacc aaaactggaa
1613

catagttctc cttcaagtgt tggcgacagc ggggcttcct gattctggaa tataactttg

1673

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1733

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1793

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1853

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1913

taagtctaaa tacaaagctg ttctgtgtga gaatttttta aaaggctact tgtataataa
1973

cccttgtcat ttttaatgta caaaacgcta ttaagtggct tagaatttga acatttgtgg
2033

tctttattta ctttgcttcg tgtgtgggca aagcaacatc ttccctaaat atatattacc
2093

aagaaaagca agaagcagat taggtttttg acaaaacaaa caggccaaaa gggggctgac
2153

ctggagcaga gcatggtgag aggcaaggca tgagagggca agttttgttg tggacagatc
2213

tgtgcctact ttattactgg agtaaaagaa aacaaagttc attgatgtcg aaggatatat
2273

acagtgttag aaattaggac tgtttagaaa aacaggaata caatggttgt ttttatcata
2333

gtgtacacat ttagcttgtg gtaaatgact cacaaaactg attttaaaat caagttaatg
2393

tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac
2453

ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg
2513

ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
2573

caggatttga gatgctaagg ccccagagat cgtttgaacc aaccctctta ttttcagagg
2633

ggaaaatggg gcctagaagt tacagagcat ctagctggtg cgctggcacc cctggcctca
2693

cacagactcc cgagtagctg ggactacagg cacacagtca ctgaagcagg ccctgtttgc
2753

aattcacgct gccacctcca acttaaacat tcttcatatg tgatgtcctt agtcactaag
2813

gttaaacttt cccacccaga aaaggcaact tagataaaat cttagagtac tttcatactc
2873

ttctaagtcc tcttccagcc tcactttgag tcctccttgg ggttgatagg aattttctct
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2993

gaaataaaat gttctgttca actt
3017

<210> 8
<211> 401
<212> PRT
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<400> 8

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20 25 30

Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln Thr Arg Ile Met Glu
35 40 45

Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu Arg Gly Ala Val Glu
50 55 60

Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu Lys Gln Arg Glu Gln
65 70 75 80

Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln Leu Glu Ser Val Asn
85 90 95

Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val Asn Asn Ile Thr Thr

100 105 110

Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln Leu Lys Thr Leu Gln
115 120 125

Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu Gln Phe Gln Lys Asn
130 135 140

Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp Leu Ser Gln Cys Ile
145 150 155 160

Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu Glu Arg Ile Glu Glu
165 170 175

Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser Arg Asp Leu Ser Glu
180 185 190

Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu Ser Glu Pro Gln Pro
195 200 205

Arg Leu Gln Ala Ala Gly Leu Pro His Thr Glu Val Pro Gln Gly Lys
210 215 220

Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr Pro Ala Pro Ser Ser
225 230 235 240

Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu Lys Glu Glu Thr Asn
245 250 255

Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg Asp Arg Leu Pro Gln
260 265 270

Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg Pro Val Gly Gly Arg
275 280 285

Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr Pro Gln Val Gln Ala
290 295 300

Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met Glu Gly Pro Glu Arg

305 310 315 320

Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu Glu Gln Glu Ala Ala
325 330 335

Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly Glu Asp Asp Tyr Asn
340 345 350

Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp Lys Gln Ala Ala Leu
355 360 365

Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn Val Glu Asp Gln Lys
370 375 380

Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu Lys Arg Asn His Thr
385 390 395 400

Leu

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<212> DNA
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<220>
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<222> (40)..(1875)
<223>

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1 5

atg gtc ctg gtg gaa att ctg gac gtg aat gac aat gtc cct gaa gta
102
Met Val Leu Val Glu Ile Leu Asp Val Asn Asp Asn Val Pro Glu Val
10 15 20

atg gtt act tca ctg tcg ctc cct gtg caa gag gat gct cag gtg ggt
150
Met Val Thr Ser Leu Ser Leu Pro Val Gln Glu Asp Ala Gln Val Gly
25 30 35

acc gtc att gcc ctg att agc gtg tcg gat cgt gac tct gga gcc aat
198
Thr Val Ile Ala Leu Ile Ser Val Ser Asp Arg Asp Ser Gly Ala Asn
40 45 50

gga cag gtc atc tgc tca ctg aca cct cat gtt ccc ttc aag ctg gtg
246
Gly Gln Val Ile Cys Ser Leu Thr Pro His Val Pro Phe Lys Leu Val
55 60 65

tcc acc tac aag aat tac tac tcg ttg gtg ctg gac agc gcc ctg gac
294
Ser Thr Tyr Lys Asn Tyr Tyr Ser Leu Val Leu Asp Ser Ala Leu Asp
70 75 80 85

cgc gag agc gtg tcg gcc tat gag ctg gtg gtg act gcg cgg gat ggg
342
Arg Glu Ser Val Ser Ala Tyr Glu Leu Val Val Thr Ala Arg Asp Gly
90 95 100

ggc tcg cct tcg ctg tgg gcc acg gct aga gtg tcc gtg gag gtg gcc
390
Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val Ser Val Glu Val Ala
105 110 115

gac gtg aac gac aat gcg cct gcg ttc gcg cag ccc gag tac aca gtg
438
Asp Val Asn Asp Asn Ala Pro Ala Phe Ala Gln Pro Glu Tyr Thr Val
120 125 130

ttc gtg aag gag aac aac ccg ccg ggc tgc cac atc ttc acg gtg tcg
486

Phe Val Lys Glu Asn Asn Pro Pro Gly Cys His Ile Phe Thr Val Ser
135 140 145

gca tgg gac gcg gac gcg cag aag aac gcg ctg gtg tcc tac tcg ctg
534
Ala Trp Asp Ala Asp Ala Gln Lys Asn Ala Leu Val Ser Tyr Ser Leu
150 155 160 165

gtg gag cgg cgg gtg ggc gag cac gca ctg tcg agc tac gtg tcg gtg
582
Val Glu Arg Arg Val Gly Glu His Ala Leu Ser Ser Tyr Val Ser Val
170 175 180

cac gcg gag agc ggc aag gtg tac gcg ctg cag ccg cta gac cac gag
630
His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln Pro Leu Asp His Glu
185 190 195

gag ctg gag ctg ctg cag ttc cag gtg agc gcg cgc gac gcc ggc gtg
678
Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala Arg Asp Ala Gly Val
200 205 210

ccg cct ctg ggc agc aac gtg acg ctg cag gtg ttc gtg ctg gac gag
726
Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val Phe Val Leu Asp Glu
215 220 225

aac gac aac gcg ccg gca ctg ctg gcg act ccg gct ggc agc gca gga
774
Asn Asp Asn Ala Pro Ala Leu Leu Ala Thr Pro Ala Gly Ser Ala Gly
230 235 240 245

ggc gca gtt agc gag ttg gta ccg cgg tcg gtg ggt gcg ggc cac gtg
822
Gly Ala Val Ser Glu Leu Val Pro Arg Ser Val Gly Ala Gly His Val
250 255 260

gtg gcg aaa gtg cgc gcg gtg gac gct gac tcc ggc tat aac gct tgg
870
Val Ala Lys Val Arg Ala Val Asp Ala Asp Ser Gly Tyr Asn Ala Trp
265 270 275

ctg tcc tac gag ttg caa ccg gcg gcg gtc ggc gcg cac atc ccg ttc
918
Leu Ser Tyr Glu Leu Gln Pro Ala Ala Val Gly Ala His Ile Pro Phe
280 285 290

cac gtg ggg ctg tac act ggc gag atc agc acg aca cgc atc ctg gat
966
His Val Gly Leu Tyr Thr Gly Glu Ile Ser Thr Thr Arg Ile Leu Asp
295 300 305

gag gcg gac gct ccg cgc cac cgc ctg ctg gtg ctg gtg aag gac cac
1014
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Thr Ala Arg Asp Gly Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val
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165 170 175

Ser Tyr Val Ser Val His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln
180 185 190

Pro Leu Asp His Glu Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala
195 200 205

Arg Asp Ala Gly Val Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val
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Gly Ala Gly His Val Val Ala Lys Val Arg Ala Val Asp Ala Asp Ser
260 265 270

Gly Tyr Asn Ala Trp Leu Ser Tyr Glu Leu Gln Pro Ala Ala Val Gly
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tcc cag aag gac tgc aac tgc ctg cac gtg gtg gag ccc atg cca gtg   249
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ctc ggg gga ccc cga gca aac aca gtc ctg gag cgt gtg gaa ggt gcc   537
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Ser Gln Lys Asp Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val
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Pro Gly His Asp Val Glu Ala Tyr Cys Leu Leu Cys Glu Cys Arg Tyr
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Glu Glu Arg Ser Thr Thr Thr Ile Lys Val Ile Ile Val Ile Tyr Leu
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Ser Val Val Gly Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val
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Asp Pro Leu Ile Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn
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Glu Glu Glu Asn Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ala Ser
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Leu Gly Gly Pro Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala
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Gly Arg Ala Gly Trp Arg Leu Leu Gln Leu Arg Cys Leu Pro Val Ala
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Arg Cys Arg Gln Ala Leu Val Pro Arg Ala Phe His Ala Ser Ala Val
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Gly Leu Arg Ser Ser Asp Glu Gln Lys Gln Gln Pro Pro Asn Ser Phe
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Ser Gln Gln His Ser Glu Thr Gln Gly Ala Glu Lys Pro Asp Pro Glu

60 65 70

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Ser Ser His Ser Pro Pro Arg Tyr Thr Asp Gln Gly Gly Glu Glu Glu
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aat tgc tcc agc cac agc aag gcc ttt gga cgc atc ctg caa cag gac    402
Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg Ile Leu Gln Gln Asp
                 90                  95                 100

att cgg gag acg gcc ttc gtg ttc gcc atc act gcg gcc ggc gcc agc    450
Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr Ala Ala Gly Ala Ser
             105                 110                 115

cac gcc gtc acg cag gcc tgt tct atg ggc gag ctg ctg cag tgc ggc    498
His Ala Val Thr Gln Ala Cys Ser Met Gly Glu Leu Leu Gln Cys Gly
         120                 125                 130

tgc cag gcg ccc cgc tgg cgg gcc cct ccc cgg ccc tcc ggc ctg ccc    546
```

```
Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg Pro Ser Gly Leu Pro
    135                 140                 145

ggc acc ccc gga ccc cct ggc ccc gcg ggc tcc ccg gaa ggc agc gcc   594
Gly Thr Pro Gly Pro Pro Gly Pro Ala Gly Ser Pro Glu Gly Ser Ala
150                 155                 160                 165

gcc tgg gag tgg gga ggc tgc ggc gac gac gtg gac ttc ggg gac gag   642
Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val Asp Phe Gly Asp Glu
                170                 175                 180

aag tcg agg ctc ttt atg gac gcg cgg cac aag cgg gga cgc gga gac   690
Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys Arg Gly Arg Gly Asp
            185                 190                 195

atc cgc gcg ttg gtg caa ctg cac aac aac gag gcg ggc agg ctg gcc   738
Ile Arg Ala Leu Val Gln Leu His Asn Asn Glu Ala Gly Arg Leu Ala
        200                 205                 210

gtg cgg agc cac acg cgc acc gag tgc aaa tgc cac ggg ctg tcg gga   786
Val Arg Ser His Thr Arg Thr Glu Cys Lys Cys His Gly Leu Ser Gly
    215                 220                 225

tca tgc gcg ctg cgc acc tgc tgg cag aag ctg cct cca ttt cgc gag   834
Ser Cys Ala Leu Arg Thr Cys Trp Gln Lys Leu Pro Pro Phe Arg Glu
230                 235                 240                 245

gtg ggc gcg cgg ctg ctg gag cgc ttc cac ggc gcc tca cgc gtc atg   882
Val Gly Ala Arg Leu Leu Glu Arg Phe His Gly Ala Ser Arg Val Met
                250                 255                 260

ggc acc aac gac ggc aag gcc ctg ctg ccc gcc gtc cgc acg ctc aag   930
Gly Thr Asn Asp Gly Lys Ala Leu Leu Pro Ala Val Arg Thr Leu Lys
            265                 270                 275

ccg ccg ggc cga gcg gac ctc ctc tac gcc gcc gat tcg ccc gac ttc   978
Pro Pro Gly Arg Ala Asp Leu Leu Tyr Ala Ala Asp Ser Pro Asp Phe
```

```
        280                 285                 290

tgc gcc ccc aac cga cgc acc ggc tcc ccc ggc acg cgc ggt cgc gcc   1026
Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly Thr Arg Gly Arg Ala
    295                 300                 305

tgc aat agc agc gcc ccg gac ctc agc ggc tgc gac ctg ctg tgc tgc   1074
Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys Asp Leu Leu Cys Cys
310                 315                 320                 325

ggc cgc ggg cac cgc cag gag agc gtg cag ctc gaa gag aac tgc ctg   1122
Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu Glu Glu Asn Cys Leu
                330                 335                 340

tgc cgc ttc cac tgg tgc tgc gta gta cag tgc cac cgc tgc cgt gtg   1170
Cys Arg Phe His Trp Cys Cys Val Val Gln Cys His Arg Cys Arg Val
            345                 350                 355

cgc aag gag ctc agc ctc tgc ctg tgacccgccg cccggccgct agactgactt  1224
Arg Lys Glu Leu Ser Leu Cys Leu
        360                 365

cgcgcagcgg tggctcgcac ctgtgggacc tcagggcacc ggcaccgggc gcctctcgcc 1284

gctcgagccc agcctctccc tgccaaagcc caactcccag ggctctggaa atggtgaggc 1344

gaggggcttg agaggaacgc ccacccacga aggcccaggg cgccagacgg ccccgaaaag 1404

gcgctcgggg agcgtttaaa ggacactgta caggccctcc ctccccttgg cctctaggag 1464

gaaacagttt tttagactgg aaaaaagcca gtctaaaggc ctctggatac tgggctcccc 1524

agaactgctg gccacaggat ggtgggtgag gttagtatca ataaagatat ttaaaccacc 1584
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<210> 6
<211> 365

<212> PRT
<213> Homo sapiens

<400> 6

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Met Leu Pro Pro Leu Pro Ser Arg Leu Gly Leu Leu Leu Leu Leu Leu
 1               5                  10                  15

Leu Cys Pro Ala His Val Gly Gly Leu Trp Trp Ala Val Gly Ser Pro
            20                  25                  30

Leu Val Met Asp Pro Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala
        35                  40                  45

Gly Arg Gln Ala Glu Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu
    50                  55                  60

Leu Ala Arg Gly Ala Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe
65                  70                  75                  80

Arg Phe Arg Arg Trp Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg
                85                  90                  95

Ile Leu Gln Gln Asp Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr
            100                 105                 110

Ala Ala Gly Ala Ser His Ala Val Thr Gln Ala Cys Ser Met Gly Glu
        115                 120                 125

Leu Leu Gln Cys Gly Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg
    130                 135                 140

Pro Ser Gly Leu Pro Gly Thr Pro Gly Pro Pro Gly Pro Ala Gly Ser
145                 150                 155                 160

Pro Glu Gly Ser Ala Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val
                165                 170                 175
```

Asp Phe Gly Asp Glu Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys
180 185 190

Arg Gly Arg Gly Asp Ile Arg Ala Leu Val Gln Leu His Asn Asn Glu
195 200 205

Ala Gly Arg Leu Ala Val Arg Ser His Thr Arg Thr Glu Cys Lys Cys
210 215 220

His Gly Leu Ser Gly Ser Cys Ala Leu Arg Thr Cys Trp Gln Lys Leu
225 230 235 240

Pro Pro Phe Arg Glu Val Gly Ala Arg Leu Leu Glu Arg Phe His Gly
245 250 255

Ala Ser Arg Val Met Gly Thr Asn Asp Gly Lys Ala Leu Leu Pro Ala
260 265 270

Val Arg Thr Leu Lys Pro Pro Gly Arg Ala Asp Leu Leu Tyr Ala Ala
275 280 285

Asp Ser Pro Asp Phe Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly
290 295 300

Thr Arg Gly Arg Ala Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys
305 310 315 320

Asp Leu Leu Cys Cys Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu
325 330 335

Glu Glu Asn Cys Leu Cys Arg Phe His Trp Cys Cys Val Val Gln Cys
340 345 350

His Arg Cys Arg Val Arg Lys Glu Leu Ser Leu Cys Leu
355 360 365

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<211> 3017
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<213> Homo sapiens

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<222> (141)..(1343)

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cgggcggcct cgtagcgggg ccccggatcc ccgagtggcg gccggagcct cgaaaagaga 120

ttctcagcgc tgattttgag atg atg ggc ttg gga aac ggg cgt cgc agc atg 173
Met Met Gly Leu Gly Asn Gly Arg Arg Ser Met
1 5 10

aag tcg ccg ccc ctc gtg ctg gcc gcc ctg gtg gcc tgc atc atc gtc 221
Lys Ser Pro Pro Leu Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val
15 20 25

ttg ggc ttc aac tac tgg att gcg agc tcc cgg agc gtg gac ctc cag 269
Leu Gly Phe Asn Tyr Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln
30 35 40

aca cgg atc atg gag ctg gaa ggc agg gtc cgc agg gcg gct gca gag 317
Thr Arg Ile Met Glu Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu
45 50 55

aga ggc gcc gtg gag ctg aag aag aac gag ttc cag gga gag ctg gag 365
Arg Gly Ala Val Glu Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu
60 65 70 75

aag cag cgg gag cag ctt gac aaa atc cag tcc agc cac aac ttc cag 413
Lys Gln Arg Glu Gln Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln
80 85 90

ctg gag agc gtc aac aag ctg tac cag gac gaa aag gcg gtt ttg gtg 461
Leu Glu Ser Val Asn Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val
95 100 105

aat aac atc acc aca ggt gag agg ctc atc cga gtg ctg caa gac cag 509
Asn Asn Ile Thr Thr Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln
110 115 120

tta aag acc ctg cag agg aat tac ggc agg ctg cag cag gat gtc ctc 557
Leu Lys Thr Leu Gln Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu
125 130 135

cag ttt cag aag aac cag acc aac ctg gag agg aag ttc tcc tac gac 605
Gln Phe Gln Lys Asn Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp
140 145 150 155

ctg agc cag tgc atc aat cag atg aag gag gtg aag gaa cag tgt gag 653
Leu Ser Gln Cys Ile Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu
160 165 170

gag cga ata gaa gag gtc acc aaa aag ggg aat gaa gct gta gct tcc 701
Glu Arg Ile Glu Glu Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser
175 180 185

aga gac ctg agt gaa aac aac gac cag aga cag cag ctc caa gcc ctc 749
Arg Asp Leu Ser Glu Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu
190 195 200

agt gag cct cag ccc agg ctg cag gca gca ggc ctg cca cac aca gag 797
Ser Glu Pro Gln Pro Arg Leu Gln Ala Ala Gly Leu Pro His Thr Glu
205 210 215

gtg cca caa ggg aag gga aac gtg ctt ggt aac agc aag tcc cag aca 845
Val Pro Gln Gly Lys Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr
220 225 230 235

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cca gcc ccc agt tcc gaa gtg gtt ttg gat tca aag aga caa gtt gag   893
Pro Ala Pro Ser Ser Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu
                240                 245                 250

aaa gag gaa acc aat gag atc cag gtg gtg aat gag gag cct cag agg   941
Lys Glu Glu Thr Asn Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg
            255                 260                 265

gac agg ctg ccg cag gag cca ggc cgg gag cag gtg gtg gaa gac aga   989
Asp Arg Leu Pro Gln Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg
        270                 275                 280

cct gta ggt gga aga ggc ttc ggg gga gcc gga gaa ctg ggc cag acc  1037
Pro Val Gly Gly Arg Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr
    285                 290                 295

cca cag gtg cag gct gcc ctg tca gtg agc cag gaa aat cca gag atg  1085
Pro Gln Val Gln Ala Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met
300                 305                 310                 315

gag ggc cct gag cga gac cag ctt gtc atc ccc gac gga cag gag gag  1133
Glu Gly Pro Glu Arg Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu
                320                 325                 330

gag cag gaa gct gcc ggg gaa ggg aga aac cag cag aaa ctg aga gga  1181
Glu Gln Glu Ala Ala Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly
            335                 340                 345

gaa gat gac tac aac atg gat gaa aat gaa gca gaa tct gag aca gac  1229
Glu Asp Asp Tyr Asn Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp
        350                 355                 360

aag caa gca gcc ctg gca ggg aat gac aga aac ata gat gtt ttt aat  1277
Lys Gln Ala Ala Leu Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn
    365                 370                 375

gtt gaa gat cag aaa aga gac acc ata aat tta ctt gat cag cgt gaa  1325
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Val Glu Asp Gln Lys Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu
380 385 390 395

aag cgg aat cat aca ctc tgaattgaac tggaatcaca tatttcacaa 1373
Lys Arg Asn His Thr Leu
400

cagggccgaa gagatgactt taaaatgttc atgagggact gaatactgaa aactgtgaaa 1433

tgtactaaat aaaatgtaca tctgaagatg attattgtga aattttagta tgcactttgt 1493

gtaggaaaaa atggaatggt cttttaaaca gcttttgggg ggtactttgg aagtgtctaa 1553

taaggtgtca caatttttgg tagtaggtat ttcgtgagaa gctcaacacc aaaactggaa 1613

catagttctc cttcaagtgt tggcgacagc ggggcttcct gattctggaa tataactttg 1673

tgtaaattaa cagccaccta tagaagagtc catctgctgt gaaggagaga cagagaactc 1733

tgggttccgt cgtcctgtcc acgtgctgta ccaagtgctg gtgccagcct gttacctgtt 1793

ctcactgaaa agtctggcta atgctcttgt gtagtcactt ctgattctga caatcaatca 1853

atcaatggcc tagagcactg actgttaaca caaacgtcac tagcaaagta gcaacagctt 1913

taagtctaaa tacaaagctg ttctgtgtga gaatttttta aaaggctact tgtataataa 1973

cccttgtcat ttttaatgta caaaacgcta ttaagtggct tagaatttga acatttgtgg 2033

tctttattta ctttgcttcg tgtgtgggca aagcaacatc ttccctaaat atatattacc 2093

aagaaaagca agaagcagat taggtttttg acaaaacaaa caggccaaaa gggggctgac 2153

ctggagcaga gcatggtgag aggcaaggca tgagagggca agttttgttg tggacagatc 2213

tgtgcctact ttattactgg agtaaaagaa aacaaagttc attgatgtcg aaggatatat 2273

acagtgttag aaattaggac tgtttagaaa aacaggaata caatggttgt ttttatcata 2333

gtgtacacat ttagcttgtg gtaaatgact cacaaaactg attttaaaat caagttaatg 2393

tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac 2453

ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg 2513

ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca 2573

caggatttga gatgctaagg ccccagagat cgtttgaacc aaccctctta ttttcagagg 2633

ggaaaatggg gcctagaagt tacagagcat ctagctggtg cgctggcacc cctggcctca 2693

cacagactcc cgagtagctg ggactacagg cacacagtca ctgaagcagg ccctgtttgc 2753

aattcacgct gccacctcca acttaaacat tcttcatatg tgatgtcctt agtcactaag 2813

gttaaacttt cccacccaga aaaggcaact tagataaaat cttagagtac tttcatactc 2873

ttctaagtcc tcttccagcc tcactttgag tcctccttgg ggttgatagg aattttctct 2933

tgctttctca ataaagtctc tattcatctc atgtttaatt tgtacgcata gaattgctga 2993

gaaataaaat gttctgttca actt 3017

<210> 8
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<212> PRT
<213> Homo sapiens

<400> 8
Met Met Gly Leu Gly Asn Gly Arg Arg Ser Met Lys Ser Pro Pro Leu
1 5 10 15

Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val Leu Gly Phe Asn Tyr

20 25 30

Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln Thr Arg Ile Met Glu
35 40 45

Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu Arg Gly Ala Val Glu
50 55 60

Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu Lys Gln Arg Glu Gln
65 70 75 80

Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln Leu Glu Ser Val Asn
85 90 95

Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val Asn Asn Ile Thr Thr
100 105 110

Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln Leu Lys Thr Leu Gln
115 120 125

Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu Gln Phe Gln Lys Asn
130 135 140

Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp Leu Ser Gln Cys Ile
145 150 155 160

Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu Glu Arg Ile Glu Glu
165 170 175

Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser Arg Asp Leu Ser Glu
180 185 190

Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu Ser Glu Pro Gln Pro
195 200 205

Arg Leu Gln Ala Ala Gly Leu Pro His Thr Glu Val Pro Gln Gly Lys
210 215 220

Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr Pro Ala Pro Ser Ser
225 230 235 240

Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu Lys Glu Glu Thr Asn
245 250 255

Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg Asp Arg Leu Pro Gln
260 265 270

Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg Pro Val Gly Gly Arg
275 280 285

Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr Pro Gln Val Gln Ala
290 295 300

Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met Glu Gly Pro Glu Arg
305 310 315 320

Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu Glu Gln Glu Ala Ala
325 330 335

Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly Glu Asp Asp Tyr Asn
340 345 350

Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp Lys Gln Ala Ala Leu
355 360 365

Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn Val Glu Asp Gln Lys
370 375 380

Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu Lys Arg Asn His Thr
385 390 395 400

Leu

<210> 9
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<212> DNA
<213> Homo sapiens

<220>
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<222> (40)..(1875)

<400> 9
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                                          Met Ala Gly His Ser
                                           1               5

atg gtc ctg gtg gaa att ctg gac gtg aat gac aat gtc cct gaa gta     102
Met Val Leu Val Glu Ile Leu Asp Val Asn Asp Asn Val Pro Glu Val
                10                  15                  20

atg gtt act tca ctg tcg ctc cct gtg caa gag gat gct cag gtg ggt     150
Met Val Thr Ser Leu Ser Leu Pro Val Gln Glu Asp Ala Gln Val Gly
            25                  30                  35

acc gtc att gcc ctg att agc gtg tcg gat cgt gac tct gga gcc aat     198
Thr Val Ile Ala Leu Ile Ser Val Ser Asp Arg Asp Ser Gly Ala Asn
        40                  45                  50

gga cag gtc atc tgc tca ctg aca cct cat gtt ccc ttc aag ctg gtg     246
Gly Gln Val Ile Cys Ser Leu Thr Pro His Val Pro Phe Lys Leu Val
    55                  60                  65

tcc acc tac aag aat tac tac tcg ttg gtg ctg gac agc gcc ctg gac     294
Ser Thr Tyr Lys Asn Tyr Tyr Ser Leu Val Leu Asp Ser Ala Leu Asp
70                  75                  80                  85

cgc gag agc gtg tcg gcc tat gag ctg gtg gtg act gcg cgg gat ggg     342
Arg Glu Ser Val Ser Ala Tyr Glu Leu Val Val Thr Ala Arg Asp Gly
```

```
                    90                  95                 100

ggc tcg cct tcg ctg tgg gcc acg gct aga gtg tcc gtg gag gtg gcc   390
Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val Ser Val Glu Val Ala
            105                 110                 115

gac gtg aac gac aat gcg cct gcg ttc gcg cag ccc gag tac aca gtg   438
Asp Val Asn Asp Asn Ala Pro Ala Phe Ala Gln Pro Glu Tyr Thr Val
        120                 125                 130

ttc gtg aag gag aac aac ccg ccg ggc tgc cac atc ttc acg gtg tcg   486
Phe Val Lys Glu Asn Asn Pro Pro Gly Cys His Ile Phe Thr Val Ser
    135                 140                 145

gca tgg gac gcg gac gcg cag aag aac gcg ctg gtg tcc tac tcg ctg   534
Ala Trp Asp Ala Asp Ala Gln Lys Asn Ala Leu Val Ser Tyr Ser Leu
150                 155                 160                 165

gtg gag cgg cgg gtg ggc gag cac gca ctg tcg agc tac gtg tcg gtg   582
Val Glu Arg Arg Val Gly Glu His Ala Leu Ser Ser Tyr Val Ser Val
                170                 175                 180

cac gcg gag agc ggc aag gtg tac gcg ctg cag ccg cta gac cac gag   630
His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln Pro Leu Asp His Glu
            185                 190                 195

gag ctg gag ctg ctg cag ttc cag gtg agc gcg cgc gac gcc ggc gtg   678
Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala Arg Asp Ala Gly Val
        200                 205                 210

ccg cct ctg ggc agc aac gtg acg ctg cag gtg ttc gtg ctg gac gag   726
Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val Phe Val Leu Asp Glu
    215                 220                 225

aac gac aac gcg ccg gca ctg ctg gcg act ccg gct ggc agc gca gga   774
Asn Asp Asn Ala Pro Ala Leu Leu Ala Thr Pro Ala Gly Ser Ala Gly
230                 235                 240                 245
```

```
ggc gca gtt agc gag ttg gta ccg cgg tcg gtg ggt gcg ggc cac gtg   822
Gly Ala Val Ser Glu Leu Val Pro Arg Ser Val Gly Ala Gly His Val
                250                 255                 260

gtg gcg aaa gtg cgc gcg gtg gac gct gac tcc ggc tat aac gct tgg   870
Val Ala Lys Val Arg Ala Val Asp Ala Asp Ser Gly Tyr Asn Ala Trp
            265                 270                 275

ctg tcc tac gag ttg caa ccg gcg gcg gtc ggc gcg cac atc ccg ttc   918
Leu Ser Tyr Glu Leu Gln Pro Ala Ala Val Gly Ala His Ile Pro Phe
        280                 285                 290

cac gtg ggg ctg tac act ggc gag atc agc acg aca cgc atc ctg gat   966
His Val Gly Leu Tyr Thr Gly Glu Ile Ser Thr Thr Arg Ile Leu Asp
    295                 300                 305

gag gcg gac gct ccg cgc cac cgc ctg ctg gtg ctg gtg aag gac cac   1014
Glu Ala Asp Ala Pro Arg His Arg Leu Leu Val Leu Val Lys Asp His
310                 315                 320                 325

ggt gag ccc gcg ctg acg tcc acg gcc acg gtg ctg gtg tcg ctg gtg   1062
Gly Glu Pro Ala Leu Thr Ser Thr Ala Thr Val Leu Val Ser Leu Val
                330                 335                 340

gag aac ggc cag gcc cca aag acg tcg tcg cgg gcc tca gtg ggc gct   1110
Glu Asn Gly Gln Ala Pro Lys Thr Ser Ser Arg Ala Ser Val Gly Ala
            345                 350                 355

gtg gat ccc gaa gcg gct ctg gtg gat att aac gtg tac ctc atc atc   1158
Val Asp Pro Glu Ala Ala Leu Val Asp Ile Asn Val Tyr Leu Ile Ile
        360                 365                 370

gcc atc tgt gcg gtg tcc agc ctg ctg gtg ctc acg ctg ctg ttg tac   1206
Ala Ile Cys Ala Val Ser Ser Leu Leu Val Leu Thr Leu Leu Leu Tyr
    375                 380                 385
```

act gcg ctg cgt tgc tca gcg ccg ccc acc gtg agc cgg tgc gcg ccg 1254
Thr Ala Leu Arg Cys Ser Ala Pro Pro Thr Val Ser Arg Cys Ala Pro
390 395 400 405

ggc aag ccc acg ctg gtg tgc tcc agc gcc gtg ggg agt tgg tct tac 1302
Gly Lys Pro Thr Leu Val Cys Ser Ser Ala Val Gly Ser Trp Ser Tyr
410 415 420

tcg cag cag agg agg cag agg gtg tgc tct gca gag agc ccg ccc aag 1350
Ser Gln Gln Arg Arg Gln Arg Val Cys Ser Ala Glu Ser Pro Pro Lys
425 430 435

acg gac ctc atg gcc ttc agc cca agc ctt cag ctg tct cga gaa gat 1398
Thr Asp Leu Met Ala Phe Ser Pro Ser Leu Gln Leu Ser Arg Glu Asp
440 445 450

tgt tta aat cct ccc agt gaa cca cga cag ccc aac cct gac tgg cgt 1446
Cys Leu Asn Pro Pro Ser Glu Pro Arg Gln Pro Asn Pro Asp Trp Arg
455 460 465

tac tct gcc tcc ctg aga gca ggc atg cac agc tct gtg cac cta gag 1494
Tyr Ser Ala Ser Leu Arg Ala Gly Met His Ser Ser Val His Leu Glu
470 475 480 485

gag gct ggc att cta cgg gct ggt cca gga ggg cct gat cag cag tgg 1542
Glu Ala Gly Ile Leu Arg Ala Gly Pro Gly Gly Pro Asp Gln Gln Trp
490 495 500

cca aca gta tcc agt gca aca cca gaa cca gag gca gga gaa gtg tcc 1590
Pro Thr Val Ser Ser Ala Thr Pro Glu Pro Glu Ala Gly Glu Val Ser
505 510 515

cct cca gtc ggt gcg ggt gtc aac agc aac agc tgg acc ttt aaa tac 1638
Pro Pro Val Gly Ala Gly Val Asn Ser Asn Ser Trp Thr Phe Lys Tyr
520 525 530

gga cca ggc aac ccc aaa caa tcc ggt ccc ggt gag ttg ccc gac aaa 1686

```
Gly Pro Gly Asn Pro Lys Gln Ser Gly Pro Gly Glu Leu Pro Asp Lys
    535                 540                 545

ttc att atc cca gga tct cct gca atc atc tcc atc cgg cag gag cct   1734
Phe Ile Ile Pro Gly Ser Pro Ala Ile Ile Ser Ile Arg Gln Glu Pro
550                 555                 560                 565

act aac agc caa att gac aaa agt gac ttc ata acc ttc ggc aaa aag   1782
Thr Asn Ser Gln Ile Asp Lys Ser Asp Phe Ile Thr Phe Gly Lys Lys
                570                 575                 580

gag gag acc aag aaa aag aag aaa aag aag aag ggt aac aag acc cag   1830
Glu Glu Thr Lys Lys Lys Lys Lys Lys Lys Lys Gly Asn Lys Thr Gln
            585                 590                 595

gag aaa aaa gag aaa ggg aac agc acg act gac aac agt gac cag       1875
Glu Lys Lys Glu Lys Gly Asn Ser Thr Thr Asp Asn Ser Asp Gln
        600                 605                 610

tgaggtcctc aaatggaaac aagccactta gccagttttt gtaataatgg caaatctctc 1935

ccatgtagca attccctgct ccttttttcct atctacatga gccctcttag agacctcaga 1995

aatctgcaga aagttccctg tgtctgtcta gaacgcattt aacaggtttt gtcgtaaaag 2055

ctttactaag tctggtgtta actctttctc tccactctgg cttgttttca gaacctaaaa 2115

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Asp Ala Gln Val Gly Thr Val Ile Ala Leu Ile Ser Val Ser Asp Arg
        35                  40                  45

Asp Ser Gly Ala Asn Gly Gln Val Ile Cys Ser Leu Thr Pro His Val
    50                  55                  60

Pro Phe Lys Leu Val Ser Thr Tyr Lys Asn Tyr Tyr Ser Leu Val Leu
65                  70                  75                  80

Asp Ser Ala Leu Asp Arg Glu Ser Val Ser Ala Tyr Glu Leu Val Val
                85                  90                  95

Thr Ala Arg Asp Gly Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val
            100                 105                 110

Ser Val Glu Val Ala Asp Val Asn Asp Asn Ala Pro Ala Phe Ala Gln
        115                 120                 125

Pro Glu Tyr Thr Val Phe Val Lys Glu Asn Asn Pro Pro Gly Cys His
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Ile Phe Thr Val Ser Ala Trp Asp Ala Asp Ala Gln Lys Asn Ala Leu
145                 150                 155                 160
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Val Ser Tyr Ser Leu Val Glu Arg Arg Val Gly Glu His Ala Leu Ser
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Ser Tyr Val Ser Val His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln
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Pro Leu Asp His Glu Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala
195 200 205

Arg Asp Ala Gly Val Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val
210 215 220

Phe Val Leu Asp Glu Asn Asp Asn Ala Pro Ala Leu Leu Ala Thr Pro
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Ala Gly Ser Ala Gly Gly Ala Val Ser Glu Leu Val Pro Arg Ser Val
245 250 255

Gly Ala Gly His Val Val Ala Lys Val Arg Ala Val Asp Ala Asp Ser
260 265 270

Gly Tyr Asn Ala Trp Leu Ser Tyr Glu Leu Gln Pro Ala Ala Val Gly
275 280 285

Ala His Ile Pro Phe His Val Gly Leu Tyr Thr Gly Glu Ile Ser Thr
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Thr Arg Ile Leu Asp Glu Ala Asp Ala Pro Arg His Arg Leu Leu Val
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Leu Val Lys Asp His Gly Glu Pro Ala Leu Thr Ser Thr Ala Thr Val
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Leu Val Ser Leu Val Glu Asn Gly Gln Ala Pro Lys Thr Ser Ser Arg
340 345 350

Ala Ser Val Gly Ala Val Asp Pro Glu Ala Ala Leu Val Asp Ile Asn
355 360 365

Val Tyr Leu Ile Ile Ala Ile Cys Ala Val Ser Ser Leu Leu Val Leu
370 375 380

Thr Leu Leu Leu Tyr Thr Ala Leu Arg Cys Ser Ala Pro Pro Thr Val
385 390 395 400

Ser Arg Cys Ala Pro Gly Lys Pro Thr Leu Val Cys Ser Ser Ala Val
405 410 415

Gly Ser Trp Ser Tyr Ser Gln Gln Arg Arg Gln Arg Val Cys Ser Ala
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Glu Ser Pro Pro Lys Thr Asp Leu Met Ala Phe Ser Pro Ser Leu Gln
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Leu Ser Arg Glu Asp Cys Leu Asn Pro Pro Ser Glu Pro Arg Gln Pro
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Asn Pro Asp Trp Arg Tyr Ser Ala Ser Leu Arg Ala Gly Met His Ser
465 470 475 480

Ser Val His Leu Glu Glu Ala Gly Ile Leu Arg Ala Gly Pro Gly Gly
485 490 495

Pro Asp Gln Gln Trp Pro Thr Val Ser Ser Ala Thr Pro Glu Pro Glu
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Ala Gly Glu Val Ser Pro Pro Val Gly Ala Gly Val Asn Ser Asn Ser
515 520 525

Trp Thr Phe Lys Tyr Gly Pro Gly Asn Pro Lys Gln Ser Gly Pro Gly
530 535 540

Glu Leu Pro Asp Lys Phe Ile Ile Pro Gly Ser Pro Ala Ile Ile Ser

545 550 555 560

Ile Arg Gln Glu Pro Thr Asn Ser Gln Ile Asp Lys Ser Asp Phe Ile
565 570 575

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